PROTEIN MALNUTRITION

PROCEEDINGS OF A
CONFERENCE IN JAMAICA (1953)
SPONSORED JOINTLY BY
FOOD AND AGRICULTURE ORGANIZATION OF
THE UNITED NATIONS (FAO)
WORLD HEALTH ORGANIZATION
(WHO)
JOSIAH MACY JR. FOUNDATION, NEW YORK

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THE FOOD AND AGRICULTURE ORGANIZATION
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JOSIAH MACY JR. FOUNDATION, NEW YORK

EDITED BY
J. C. WATERLOW

CENTRAL FOOD TECHNOLOGICAL RESEARCH INSTITUTE, * MYSORE. *
22 OCT. 1955
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PRINTED AT THE
UNIVERSITY PRESS, CAMBRIDGE
FOR
THE FOOD AND AGRICULTURE ORGANIZATION
WORLD HEALTH ORGANIZATION
JOSIAH MACY JR. FOUNDATION
1955

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Printed in Great Britain at the University Press, Cambridge
(Brooke Crutchley, University Printer)

CONTENTS

FOREWORD *page* vii

INTRODUCTION xi

LIST OF PARTICIPANTS xv

FIRST SESSION
Biochemical Aspects of Protein Malnutrition 1

SECOND SESSION
Pathology of Protein Malnutrition 68

THIRD SESSION
Clinical Aspects and Treatment of Protein Malnutrition 137

FOURTH SESSION
Epidemiology and Prevention of Protein Malnutrition 224

PLATES 1–24 *at end*

FOREWORD

This conference on protein malnutrition in Jamaica was sponsored by the Food and Agriculture Organization of the United Nations (F.A.O.), the World Health Organization (W.H.O.) and the Josiah Macy Jr. Foundation, which contributed a large share of the cost. It will be of interest to indicate some of the events which preceded the convening of this conference, which differed in several ways from the pattern of the conferences usually organized by F.A.O. and W.H.O.

The Joint F.A.O./W.H.O. Expert Committee on Nutrition at its first session in October 1949 drew attention to the problem of protein malnutrition (although the term was not in use at that time), and commented that 'one of the most widespread nutritional disorders in tropical and subtropical areas is a syndrome at present ill-defined, known by various names such as "kwashiorkor", malignant malnutrition, polydeficiency disease, "m'buaki", syndrome dépigmentation-œdème, infantile pellagra, etc.'. It recommended that W.H.O. should conduct an inquiry into the various features of kwashiorkor with the object of collecting information on the epidemiological and sociological aspects of the syndrome.

The Second Session of the Joint Committee in April 1951 considered the problem in greater detail. It had before it the survey of kwashiorkor in Africa made in 1950 by J. F. Brock (W.H.O. consultant), and M. Autret (Nutrition Division, F.A.O.). Further surveys of a similar kind were recommended. The Committee also stressed the need for disseminating information on kwashiorkor, and considered preventive measures. It listed under various heads the further investigations which seemed to be most needed.

In the second half of 1951 a survey of kwashiorkor in Central America was made by M. Autret and M. Behar of the Institute of Nutrition for Central America and Panama. A similar survey was made in 1953 in Brazil by J. Waterlow (acting as W.H.O. consultant), and by A. Vergara (Nutrition Division, F.A.O.).

The third Session of the Joint F.A.O./W.H.O. Expert Committee on Nutrition, held in the Gambia, West Africa, in November 1952, was devoted entirely to malnutrition in mothers, infants, and children. It was at this meeting that the term 'protein malnutrition' was introduced into current use. The session of the Joint Committee followed a conference convened in the same place by the Commission for Technical Co-operation in Africa South of the Sahara (C.C.T.A.), concerned with the same theme with reference to Africa. The Joint Committee found it difficult to define the terms kwashiorkor and protein malnutrition, and to distinguish between under- and malnutrition as causal factors. Partly because they realized that clarity on these and other points had not been achieved, the Committee recommended that further meetings on protein malnutrition should be held in different regions. It also referred to the need for co-ordination and continuity of work in this field, and to the contribution which F.A.O. and W.H.O. can make in this direction.

Protein malnutrition figured prominently on the agenda of two F.A.O./W.H.O. regional nutrition meetings held in 1953, namely the Nutrition Committee in South and East Asia (Bandung, June 1953), and the Third Conference on Problems of Nutrition in Latin America (Caracas, October 1953). The Bandung Committee dealt with the features and aetiology of protein malnutrition; its treatment; its long-term effects on community health; the further investigations needed; prevention through food production, distribution, and processing programmes; public health measures and education. The Caracas Conference also reviewed the subject at length and recommended appropriate measures for prevention and treatment.

These international discussions and surveys reflected the growing interest in the problem of governments, public health authorities, physicians and research workers in many parts of the world. They made it possible for workers from many lands to meet and present their results. However, as more information accumulated from different countries about the clinical, biochemical and pathological features of protein malnutrition, it became apparent that in spite of the basic similarity of the syndrome throughout the world, there were many points on which general agreement had not been reached. In part this might result from geographical variations in the characteristics of the disease, in part from differences in method and approach, in part again from differences in interpretation. In this situation it seemed desirable to arrange for a conference or working-party at which purely scientific and technical discussions would be held, without the necessity for making agreed recommendations. Jamaica was a convenient site, since pioneer work on protein malnutrition and allied problems had been done there. For a meeting of this kind the informal technique of the Macy Conferences appeared to be well suited.

We wish to express, on behalf of F.A.O. and W.H.O., our gratitude to the Josiah Macy Jr. Foundation and to Dr Fremont-Smith, its Medical Director, for co-operation in the conference. The presence of Dr Fremont-Smith, with his experience in guiding discussions of this kind and in resolving philosophical tangles, was of great value, and it was unfortunate that he was only able to stay for the first two sessions. Grateful acknowledgment is also due to the Government of Jamaica and to the University

College of the West Indies, to the members of the staff of the College who were responsible for the administrative arrangements, and to the Committee of the Senior Common Room who put their rooms at the disposal of the conference. In particular we wish to thank Dr Clements, the Chairman of the Conference, and Dr J. Waterlow, who did much of the preparatory work for the meeting, undertook the laborious task of editing its report, and has written the Introduction.

W. R. AYKROYD
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Food & Agriculture Organization

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INTRODUCTION

This conference, in its four sessions, deals with the biochemistry, pathology, clinical aspects, treatment, and prevention of protein malnutrition. It was not intended to cover these fields in detail and *in extenso*, since this had been done at previous conferences. The object was rather to clarify points of difference, and to put up new ideas for discussion and challenge.

For this purpose the most suitable type of meeting seemed to be that which over the last ten years has been developed with conspicuous success by the Macy Foundation. At these Macy conferences there are no formal agenda, interruption is encouraged, and discussion is unorganized and free. The *raison d'être* of this type of conference is the belief that it is far more effective than a formal series of papers in breaking down psychological barriers to the exchange of information and ideas. How often is the remark not heard that the main benefit of a conference comes from the talks at the bar or the lunch-table, outside the conference room? By the Macy technique these talks become the conference. The method is perhaps particularly useful when many disciplines are represented. This conference was composed, in more or less equal parts, of administrators, clinicians and laboratory workers in various fields.

Both for the Macy Foundation and for the International Organizations the Jamaica conference was something of an innovation. For F.A.O. and W.H.O. it went against the grain at first to embark on a conference with no fixed agenda and no clearly determined objective. At the Macy conferences, although it is a principle that many disciplines should be represented, it has not been usual to gather round one table participants of so many different nationalities. All the discussions were in English, and the English-speaking members were most grateful to their French, Spanish, and Portuguese-speaking colleagues for generously foregoing their own languages. If the success of the conference is to be judged from this report, these growing pains inevitable in any new development must be taken into account.

Throughout all the sessions runs the underlying difficulty of defining and clarifying terms such as protein malnutrition and kwashiorkor. After the third session, for instance, the reader may feel: 'This is all very interesting, but I still do not understand what should be considered the diagnostic features of protein malnutrition.' This difficulty, however, is not unusual in human affairs; in fact, it is the rule rather than the exception. The problem was originally posed by Zeno in pre-Socratic times, when he asked 'When do we describe a bald man as bald?' If we were investigating the matter scientifically we might agree on a definition that a person should be considered bald when the number of hairs per square inch falls below a certain figure. In practice, however, this is not what is done. We all recognize a bald man when we see him, and if pressed the best definition that we could give would be something like this, that 'a person is bald when there is more of his head without hair than with'. A more precise definition, by counting hairs, is conceivable but is not in fact used in ordinary life. Moreover, such a definition does not cover the case of the investigator who says: 'This subject is not actually bald, but from various signs I consider that he is about to go bald. I shall therefore call him pre-bald, and place him in the same group as those who are actually bald.' This statement naturally causes an outcry among those who maintain, not without reason, that if you make a definition you should stick to it. Yet the advocate of the concept of pre-baldness has a valid point when he says: 'There must be some stage which leads up to baldness; it is much more important to recognize this stage and deal with it than to concentrate on the heads which are actually bald.'

This is the situation with kwashiorkor and protein malnutrition. In ordinary life we know what kwashiorkor means and can often diagnose it without hesitation. But this rough usage is not enough when it comes to accurate description and classification. The difficulty, however, can be resolved by following the advice given by Dr Fremont-Smith in the first session, that with any definition it is necessary to bear in mind the purpose for which that definition was made. The name kwashiorkor is generally used as a *clinical* definition – as a symbol to conjure up a certain clinical picture. It is true, as this conference has shown, that this picture is not identical in the minds of all observers. For this reason Dr Fremont-Smith suggested that all the participants at the meeting should submit for publication complete case-sheets of kwashiorkor as they see it in their area. This, unfortunately, has not proved feasible, but the same objective would be achieved if all who publish descriptions of the disease were to state clearly the nature of their criteria. In many published accounts this has, of course, been done; what has been done less often is to give any description of the cases which, for one reason or another, the author does not include in his group 'kwashiorkor'. This negative side of the picture may be as important as the positive side; for instance, the statement is sometimes made that all cases of kwashiorkor have oedema, but nothing is said about the nature or frequency of cases with some of the other features of the syndrome, but without oedema.

An ideal account of kwashiorkor might, it is suggested, fall into three parts

(i) A description of cases called kwashiorkor, with their features tabulated to indicate their frequency.

(ii) A description of cases which are believed to be of the same fundamental nature, but which, for reasons stated, are not included in the kwashiorkor group. If these are thought to represent the early stages of the syndrome they can legitimately be called 'pre-kwashiorkor' for purposes of classification.

(iii) A description of cases of malnutrition or other similar conditions which, for reasons stated, do not fall into the kwashiorkor group, and should be distinguished from it.

An example of such an approach is the division made by Jelliffe and Stuart of malnourished infants in Jamaica into three groups—kwashiorkor, marasmic kwashiorkor and marasmus. Such a method of description leaves little room for misconceptions.

If reports are made in the way that has been suggested there can be no dispute about the facts, since these facts will not be biased by selection. The problem then becomes one of interpretation. This problem has often taken the form: what are the fundamental features of kwashiorkor? What are the essential diagnostic criteria? If this question is argued purely on the descriptive plane it becomes a dispute about labels, which is clearly sterile, since every author has a right to select whatever labels suit him best for classifying his cases. But if the question is put in the form: 'What is the fundamental process going on in these cases that are called kwashiorkor, that distinguishes them from those that are not called kwashiorkor?', then it is full of meaning.

The term protein malnutrition was introduced in an attempt to tackle the problem in this way. Protein malnutrition is regarded as a process operating in cases of kwashiorkor, and perhaps also in many others which would not be classified as kwashiorkor—at least not by all workers. It is therefore a wider term than kwashiorkor, and also a different kind of term. This much was agreed by the conference.

Unfortunately, the connotation of the words 'protein malnutrition' is somewhat vague. The next stage is to obtain further information about the nature of the process, so that it is possible to determine when it is present and when not. Since malnutrition is not an all-or-nothing effect but a matter of more-or-less, this information must in the long run be quantitative. It will be for the reader to judge how far the conference was successful in giving some insight into the nature of this process, and in producing fruitful ideas for further work.

J. WATERLOW

LIST OF PARTICIPANTS

Dr F. W. Clements, Institute of Child Health, Royal Alexandra Hospital, Camperdown, N.S.W., Australia. (*Chairman.*)

Dr M. Autret, Nutrition Division, Food and Agriculture Organization, Rome.

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Dr G. R. Bras, Department of Pathology, University College of the West Indies, Jamaica.

Dr R. C. Burgess, Chief, Nutrition Division, World Health Organization, Geneva.

Professor E. K. Cruickshank, Department of Medicine, University College of the West Indies, Jamaica.

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DR G. WILSON, Nutrition Officer, Jamaica.

FIRST SESSION

BIOCHEMICAL ASPECTS OF PROTEIN MALNUTRITION

CLEMENTS (*Chairman*): This begins the first of the technical sessions. On certain days certain subjects will be discussed. Today the subject is biochemistry, but I think it would be a tragedy if we limited our thinking today to biochemistry. It seems to me that all of us are aware of the wider implications of this problem, and that there will be stirrings within us from time to time to get away from the specified subject of the hour. I suggest that you give way to the impulse and interrupt, even though your remarks may happen to be about prevention in the middle of an exposition on enzymes.

I am now going to ask Dr Waterlow to introduce the discussion.

WATERLOW: Dr Fremont-Smith has said in the past that speakers at the Macy conferences fall into three categories: those who do not want to be interrupted at all, those who wish to be interrupted at stated points, and those who are prepared to be interrupted at any time. I am going to take a chance and put myself in the third category.

For me this conference or meeting is probably the most important of any that I have attended, not because we have had to organize it, but because of what I expect to learn from it. It is all the more difficult to have to set the ball rolling, but as it is an informal meeting I might perhaps begin on a personal note.

The subject of this day's session is the biochemical aspects of protein malnutrition. My own work has been mainly in that field; it is laboratory work, and yet it is the patients who are the mainspring of my efforts. Without the clinical material the laboratory studies have little meaning for me. Thanks to Professor Cruickshank I have the care of some babies in the hospital here, and in spite of all that has been done and written on kwashiorkor or protein malnutrition, and in spite of what I consider to be very efficient hospital services, time and again we have difficulty in curing these cases. That, to me, is the challenge for the scientific work.

Admittedly, when I refer to cases or patients, I am talking of babies who are ill; I realize very well that we are concerned not only with the very sick and the dying, but perhaps much more with mild or chronic, so-called 'marginal', states of malnutrition in infants and children. I know that from the point of view of the world as a whole and the happiness of the greatest number of people, this is a far more important problem than acute kwashiorkor. But I think there is plenty of justification in the history of medical science for proceeding from the study of the very bad to the less bad cases; therefore I would like to make it clear that, although I am mainly talking about the seriously ill baby, it is not from lack of interest in the less ill, but only because by this means I hope to find the quickest way to the heart of the problem.

Dr Fremont-Smith asked us to speak of our personal work, but I hope that it may be in order first to try and analyse shortly some of the concepts with which we have to deal. I also think that in some ways it is more important to talk about the work that has not been done than the work that has been done.

When I look back to the C.C.T.A. conference and the meetings of the Expert Committee that were held a year ago in the Gambia(1) it seems to me that the introduction of the term 'protein malnutrition', which, as far as I know, was first used at those two conferences, was a considerable step forward. As is obvious, these words signify a *process*, whereas 'kwashiorkor' and all the other names that have been used for the syndrome, except perhaps 'infantile pellagra', are *clinical* terms conjuring up a certain collection of signs and symptoms. Any concept, like that of protein malnutrition, which is essentially a hypothetical description of a possible process may be true but it may not necessarily be useful. We have to ask: does it lead to a clearer theoretical understanding and a better practical control of the problem? If the concept is to be useful, first of all I think it is most important not to get confused between two different planes on which we think and use words—the descriptive or clinical plane on the one hand, and the analytical or causal on the other.

In the Gambia I think we did get into some trouble on this point, in confusing the two planes of thought, because there are two quite different arguments. One is the clinical argument: when does one diagnose kwashiorkor, marasmus, or whatever it may be, and when does one not diagnose it? The other is an argument about pathogenesis and the nature of the underlying process.

It is obvious that the first argument, that of clinical description and diagnosis, can be properly settled only when the second question has been answered. Nevertheless, we cannot shelve this clinical problem; for practical purposes we have to consider descriptive and diagnostic criteria. It was clear to me, from the work that Vergara, Santos and I did in Brazil(2), that the comparative reporting of facts on the purely clinical plane was useful and must be continued.

At the Gambia conference Trowell(1) suggested that the essential constant features of kwashiorkor are a diminution in pancreatic enzyme production and a good response to treatment with milk protein. I find this confusing; on the clinical plane it does not seem to clarify the distinction between kwashiorkor and marasmus.

Rao: I think the confusion still exists. The point raised at the conference was that in protein malnutrition it is only the protein factor which has dropped down, whereas all the other factors are still there. But this does not give a clinical distinction from general undernutrition or marasmus.

Clements: Trowell also insisted that kwashiorkor was accompanied by a relative increase in carbohydrate intake.

Williams: It seems to me that a great many cases of marasmus are not due purely to defects in the food, but to mixed bacterial infection, which sometimes may have caused irreversible damage to the intestine. You may not be able to identify the bacteria because they have eliminated themselves by overproduction. But I am quite certain that infection does play a large part in a good many of the marasmus cases, whereas you can get many cases of kwashiorkor without any history of infection.

Clements: Would you like to proceed, Dr Waterlow?

Waterlow: Yes, so long as I am not suppressing any interruptions.

Fremont-Smith: One further word; it seems to me that this kind of conflict is one that recurs frequently in science; you made a distinction between the clinical approach and consideration of the nature of the process. It seems to me that one very helpful way of dealing with this kind of situation is to have the person presenting a point of view bear in mind and specify the purpose for which it is presented. There is a general tendency for us to take an attitude toward a disease or toward a problem and generalize that this is the attitude to take, whereas somebody else says: 'No, *this* is the attitude to take.' If we will specify quite clearly the purpose for which we are using a certain phrase or a point of view, I think the problem will be partly solved; everyone will see that in the clinical situation, as you said, even though we have incomplete knowledge, we have to classify cases clinically for very practical purposes. That goal is quite different from the goal of trying to understand a process, because there you may have three or four different concepts, which may be contradictory or may come from different scientific disciplines. If, instead of allowing ourselves to generalize, we specify the purpose for which a point of view is being presented, I think that these differences tend to disappear. Each statement is useful within a narrow context of purpose and may not be useful outside that context.

Waterlow: You have put exactly what I was trying to say; a definition or description such as the one I quoted may very well be true, but in the context of the Gambia conference we were concerned—or at least so it seemed to me—with helping clinicians and physicians all over the world to describe and tell us about the frequency of this condition, its local characteristics, etc. I felt that it was not clear what kind of a definition Dr Trowell was trying to make. On the clinical plane, if the diagnostic criteria are stated to be changes in pancreatic enzyme secretion and response to treatment, it is very little help to the man in the field. On the theoretical plane it is debatable whether the features that he regards as essential are in fact characteristic of a specific process, present in kwashiorkor and absent, for example, in marasmus.

DEAN: I think there is another way of looking at it. The position of the clinician and the position of the biochemist are not necessarily so separate as you seem to imply. I find, looking at the literature and the way this disease has been approached in many places, that there is a great deal of confusion, which has been partly brought about by the question of the role of infection. It is our job as biochemists, or as people who can at least provide some objective measure, to help the clinician to make the diagnosis. The diagnosis seems to be made without any real background of scientific fact—a gap which I think this conference should try to remedy.

WATERLOW: I don't agree with that. I don't think there is such a thing as 'the' diagnosis.

DEAN: I think there may be.

WATERLOW: At least, that is the position that I hope to put forward.

FREMONT-SMITH: I think we suffer—at least I have suffered—from the traditional educational concept of single causes in medicine. It seems to me that in biology in general we still have not caught up with the physicists who have long ago left single causality behind and deal with the Gestalt, with a constellation of events in time and place, and with multiple causes.

SCRIMSHAW: Although it isn't fair to say this in advance of your presentation of biochemical results, in I.N.C.A.P.* we are far from convinced that the biochemical changes encountered are specific to protein malnutrition; rather, they seem to be non-specific. Do you find evidence of specific changes?

CLEMENTS: Aren't you judging the case before it is presented?

WATERLOW: The point I am really trying to make is this: I myself am very much interested in clinical classification and the collection of clinical facts, but today and at this moment, I am not concerned with that. I am trying to examine what is the *process* which we think may be present; analysing the process is a different matter from diagnosing the clinical syndrome.

I want to try, in a very simple way, to examine this concept of protein malnutrition. What does it mean, or what does one expect those words to mean? It is obviously a complex concept. First of all it implies a simple shortage of dietary protein; secondly, as many people cautiously pointed out at the Gambia conference, it may include a shortage of other substances involved in protein metabolism and synthesis, such as members of the vitamin B complex and perhaps unknown substances. I do not intend to go into this aspect in detail. But, complex though the aetiological factors may be, the end result is *protein depletion of the body and failure of protein formation in the growing organism.* Whatever the detailed sequence of events, that, it would seem to me, is what one means when one says 'there is a person with protein malnutrition'.

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* Institute of Nutrition for Central America and Panama.

Fremont-Smith: Do you give special emphasis to the growing organism?

Waterlow: Yes.

Fremont-Smith: Then wouldn't it be useful to call this protein malnutrition in the growing organism, or in the child?

Waterlow: I don't know whether the end results are qualitatively the same in the growing child and the adult. That remains to be seen. But will you accept protein depletion as the end result, however it is brought about?

Gyorgy: I don't accept it.

Rao: But, Dr Waterlow, do you include the effect of a low intake of protein also?

Waterlow: I am saying that a low intake either of protein or of factors influencing protein synthesis will lead to an organism depleted of protein.

Gyorgy: I can't accept that. What do you do in complete starvation? Would you not lose protein too?

Waterlow: Of course.

Gyorgy: And you would still call that protein malnutrition?

Waterlow: Could you give me 2 minutes to come to that point?

Gyorgy: I just raised my objection, that's all.

Rao: I believe Professor Gyorgy raised the question in the Gambia of the low protein content of mother's milk, and therefore it is not a question of protein alone, but there may be an imbalance in the amino-acid composition.

Waterlow: I am not now talking about causes, Dr Rao. I am talking about what happens in the organism. I am not talking about what leads up to it, whether it is an imbalance of vitamins, amino acids, total intake, or anything else. I am trying to analyse the concept of the organism which is short of protein. Maybe that is an artificial thing to do, but that is the way I am trying to tackle the problem. It seems to me that if we could get a clear picture of the end result, or, if you like, the different possible end results, then we could get back to considering the causes of it.

Fremont-Smith: When you spoke of including the failure of building blocks or essential factors in protein metabolism, you would include a lack or imbalance of amino acids?

Waterlow: Yes. The point I want to emphasize—it seems to me very obvious, and I can't see why anyone should object to it—is the concept of an organism which by some means or other has become depleted of protein or failed to gain protein as it should during growth.

There are two additional ideas which have become attached to this concept in its application to kwashiorkor. One is that the condition of protein depletion, whatever its nature, is modified by the concomitant calorie intake. That is an idea, as you know, that has been especially emphasized by the Uganda school. The second is the hypothesis which I put forward in 1949(4), that the effects of this depletion are most felt in the organs with the highest protein turnover. That is a sort of subsidiary hypothesis to which I have nothing further to add at the moment, nor do I intend to say anything in detail about the possible ways in which a condition of protein depletion might be brought about. I think many people in the conference will have much more to say about that. At present I am concerned with the condition once it is established, and it seems to me that there are three questions raised, which lead on to the work we have been doing here.

The first is, what are the effects of protein depletion on the organism?

Secondly, how do the calorie intake or other factors modify these effects?

Thirdly, how can protein depletion be detected, assessed, and measured in man?

I want to deal with those three questions one by one, although they are not unconnected.

Gyorgy: Are you now identifying or substituting protein depletion for protein malnutrition?

Waterlow: No, I am saying that presumably protein malnutrition leads to protein depletion. Protein depletion is the state of the organism.

Gyorgy: It leads to one kind of protein depletion. I would accept that.

Waterlow: I am trying to consider what different kinds there may be.

Gyorgy: All right; if you will define them, then I will desist from further comment.

Waterlow: I will do my best. It seems to me, judging from what I have read or seen, that the first and most obvious effect or characteristic of this state of protein depletion is a reduction in protein content and active cellular mass in most organs of the body, a reduction which varies in degree with different organs. The blood, for instance, can be counted as an organ. There may be hypoproteinaemia, and in clinical work we constantly look for this as a sign of protein deficiency. It is, indeed, often present in infants, much less often in adults. Even where there is no hypoproteinaemia there may be a decrease in plasma volume, and so in total circulating plasma protein. However, measurement of protein levels, even when combined with estimates of plasma volume, are a poor guide to the state of the body as a whole, since, according to the experimental work of Alison(5) and others, in animals depleted of protein thirty times as much body nitrogen is lost from the soft tissues as from the plasma proteins. Therefore the loss from the blood is such a small proportion of the whole that it is a bad guide to the degree of depletion.* Clinically, and through the microscope, we can see evidence of loss of protein from some of the soft tissues. Muscles are small and atrophic(6), and there is atrophy of the acinar cells of the pancreas, and of the intestinal epithelium(7, 8). I shall produce evidence that the liver shares in this loss. Clinical observation agrees with the results of animal experiments in suggesting that the loss is worst, and the damage greatest, in liver, pancreas and gut. As I have said, I imagine that this is because of their rapid protein turnover. As you know, the Rittenberg school(10) have made measurements in man, from which they deduce that the half-life of liver proteins is approximately 12 days, whereas the half-life of the proteins in what the biochemists call the carcass (by which they mean mainly muscle and skin, I think) is about 80 days.

I think we must accept this concept of the loss of protein from all organs in varying degree and at varying rates. Moreover, as far as we know, there is no such thing as a storage protein, but only protein that is mobilized with greater or less ease. Thus depletion must mean a loss of active cytoplasm. This point has been often raised and has been emphasized by Kosterlitz(11) and others; presumably this loss leads to functional changes in the organs so depleted.

DEAN: Has the loss ever been measured in kwashiorkor? It has been measured in the blood, but has it been measured in anything else?

WATERLOW: Not as far as I know. I have a certain amount of evidence, which I am going to produce later, about the liver, but at the moment I am basing my remarks mainly on experimental work on protein-depleted animals. This is what we would expect from the experiments. The depletion seems to lead to functional changes, such as loss of pancreatic enzymes, changes in blood enzymes, changes perhaps in various functions of the liver. But these effects, which no doubt will be described in greater detail at this conference, are manifestations of the functions of particular organs only. We cannot extrapolate from them to the body as a whole. I do not believe that this is possible from any of the measurements that have yet been done. An example is the plasma choline esterase, in which I have been interested for a long time, having begun work on it in the Gambia; I think this enzyme is formed in the liver, and I think that the low levels found in the blood and liver of malnourished infants(12) indicate the difficulty the liver has in synthesizing this protein. But it would be rash to generalize and say that this particular measurement gives any clear and accurate indication of the protein nutrition of the body as a whole. It gives perhaps as good a one as any other measurement. At the moment we cannot go further.

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* Moreover, as is well known, Whipple and his colleagues(9) showed, many years ago, that tissue proteins could contribute to the formation of plasma proteins, the production of which seems to have a high priority. Contrariwise, when plasma proteins are given to a depleted animal, they are retained for the most part in the tissues. In malnourished infants given plasma transfusions, we have always observed that the rise in plasma protein level is far less than would occur if all the injected protein had been retained in the circulation.

If you will accept the idea that the cardinal result of low protein intake or protein depletion is a loss of active cytoplasm from organs in varying degrees, then the next question that arises is whether states of protein depletion differ only in severity or whether they also differ in kind.

I believe there is plenty of experimental evidence that they can differ in kind. Single amino-acid deficiency produces effects different from total protein deficiency(13); some of the experiments of Whipple and his colleagues suggest that when an incomplete protein or mixture of amino acids is fed, the body proteins may be raided to provide constituents for the blood proteins(9); in other words, we have to include in our concept of protein depletion the idea that there may be different *patterns* of depletion under different dietary conditions. We cannot assume that, whatever the mechanism, the end result is always the same. I am sure that there must be different patterns. There does, for instance, seem to be a very considerable difference between the findings in infants and in adults. But can we say that under certain conditions the pancreas is affected, and under certain conditions it is not, and so on? As yet I think not.

For the moment we must leave that point and come on to the question of the influence of the calorie intake on protein depletion. You are all familiar with the kind of dichotomy that was made at the Gambia conference between marasmus and kwashiorkor. The view seems to be implied by some that in marasmus you do not find the specific changes which are typical of kwashiorkor, such as fatty liver, pancreatic changes and oedema. Marasmus is associated with a low calorie intake, which in some way protects, as it were, against these specific effects. The suggestion was made that 'the marasmic infant lives on its own meat'—in other words, that it gets meat not from the outside but from its own muscles to protect its liver and pancreas.

RAO: If any meat is left.

WATERLOW: It starts with having some meat, I suppose. But it is difficult to accept this as an explanation, because we all know that on a low protein intake, whatever the calorie intake, there will be a negative nitrogen balance;

as you increase the carbohydrate intake, the negative balance is reduced, and the loss of nitrogen is less. That has been so amply shown, both in many kinds of animals and in man, that I don't think anybody could dispute the fact, whatever the mechanism may be (14). There is the possibility, I will admit, that when muscle protein is broken down to provide energy, the blood stream is flooded with amino acids and some of this flood might be mopped up by vital organs such as the pancreas and the liver; in fact, there might be a raiding of other tissues to protect these organs, but I don't think there is any experimental evidence in favour of such a conclusion, at least as far as I know.

Gyorgy: Sure, there is experimental evidence. You can produce it in rats at any time.

Waterlow: Produce what?

Gyorgy: Marasmus or complete inanition and starvation, and you will never get changes in the liver. They will die with a normal, small, atrophic liver.

Waterlow: Exactly, a small atrophic liver. But is that a normal liver? Addis (15), for instance, showed that in a starved rat after 2 days there was 20% loss of liver substance, and after a week 40% loss.

Gyorgy: That is true, but if you were to add calories in the form of carbohydrate, then you would get a fatty liver.

Waterlow: That is a different point though.

Gyorgy: How is it different?

Waterlow: It is a different point in this sense: the question that I am raising is not whether the liver is protected from fat, but whether it is protected from loss of protein by the breakdown of muscle during starvation.

Gyorgy: But it is protected in a sense, because it is a normal, small liver.

Waterlow: I don't see how you can call a small liver a normal liver.

Gyorgy: Then I must ask you to call on the pathologist and see whether he would say whether the cells are normal or abnormal, or in what respect—to use Dr Fremont-Smith's term again—the liver is abnormal, and in what respect the rat that received the small amount of protein, but added calories, would have a different liver.

Cruickshank: The pathologist can only say that it looks normal.

Clements: Within the limits of his technique.

Gyorgy: Well, the clinicians are in a worse position. The clinicians cannot even say that.

Fremont-Smith: But if you don't use the word 'normal', if you just say that there are different kinds of changes in the liver, neither of them need be called normal, so you are not caught by that awful word.

Gyorgy: Yes, that is right.

Waterlow: I quite agree with you. The point I mean to make is that this liver in the starved rat has lost 40% of its substance. It is a protein-depleted liver and, as far as I know, it is not protected from the depletion by the great loss of protein from the muscles.

Fremont-Smith: I think everybody would have to agree that it is a protein-depleted liver, but one could argue whether the individual cells of that liver are protein depleted; and it seems to me that this may be a possible distinction.

Waterlow: There is evidence in the literature and from our own work that they are protein-depleted (11, 16).

Gyorgy: Yes, but it is still a different kind of liver. It is protected from becoming fatty.

Cruickshank: Only one of two things, as I see it, can have happened. Either there must have been a reduction in the total number of cells in that liver, or else there must have been a selective or overall reduction in the size of the cells.

Fremont-Smith: Or both.

Cruickshank: And that in itself is abnormal. Can the pathologists tell us the answer to either of these questions? Is there a reduction in the total number of cells in the marasmic or purely starved animal, or can they measure a reduction in cell size?

Mackay: It has been repeatedly observed in physiological adaptations that the cell number does not change but the size does. A typical example is the case of the heart. I should have thought it rather unlikely, in the case that Dr Waterlow is describing, that the liver just loses 50% of its cells.

Waterlow: It does not. It loses its cellular cytoplasm. The cell number remains unchanged (11, 16).

Mackay: One other point is the judgement of cell size. I have tried to do this at one time or another, and find it extremely difficult. Following the process of fixation, can you say that what you see is the size of the normal cells?

Bras: It is an extremely difficult point, as you say. Tissues which have been processed in a normal way do suffer from shrinkage, and it would require special precautions if you want to make measurements. Of course, you can get comparative figures, disregarding the matter of absolute shrinkage.

Mackay: So we are finally left with the point that it is really an intracellular change.

Waterlow: We are agreed, then, that judging by the experimental work, if an animal is starved its liver will be decreased in weight by about 40%, and there will be a parallel loss in liver protein. This is brought about not by reduction in number of cells, but by a loss of cytoplasm from each cell. That is one condition. If a similar animal is put on the same protein-free diet, but with added calories, it would admittedly have more fat in its liver; but would that liver be more protein-depleted or less than in the starved animal? I think that it would be less depleted.

It seems to me that the higher calorie intake *must* protect the organism against the loss of protein. Admittedly it may do many other things as well. I entirely agree with Dr Gyorgy, and I argued this many years ago after my first work in the West Indies (6), that on all theoretical grounds the higher the calorie intake the more you would tend to get a fatty liver. In that sense the higher calorie intake may be harmful. It may also, judging by Dr Burgess's (17) observations in Singapore, promote the signs of riboflavin deficiency.

GYORGY: Or any vitamin deficiency.

SCRIMSHAW: As you know, this carries over to blood levels. We find reduced serum levels of protein and of most vitamins and reduced alkaline phosphatase levels in children with kwashiorkor; but in experimental animals, starved to the point where they are dying, you may find no changes at all. We have recently confirmed this for completely starved hens for a group of nine blood constituents.

WATERLOW: What I am trying to say is that a higher calorie intake should, on theoretical and experimental grounds, protect against loss of nitrogen, whatever else it may do. It may promote fatty liver, or it may promote a vitamin deficiency, but it should reduce nitrogen loss.

GYORGY: Well, there is one important problem, which is a problem for the future perhaps; at least I don't know of any old studies on it; that is, whether you can say that with a higher calorie intake protein retention must increase in all organs or maybe only in the muscles.

WATERLOW: I don't know.

GYORGY: The liver and pancreas, where the changes will certainly be enhanced, may lose more protein when you add more calories to the diet. I personally am inclined to believe that when you add more calories to a low protein diet you get more nitrogen retention, but the nitrogen may go to the muscle.

WATERLOW: Yes, I would entirely agree that according to the conditions—the nature of the protein deficiency or imbalance and the adequacy or otherwise of the calorie and vitamin intake—we may have many patterns of depletion which we really know practically nothing about, even experimentally.

FREMONT-SMITH: Isn't there a very clear experiment that could be done here? If you took a comparable series of rats, one group of which was simply starved, and the other group given calories but no protein, and then if total liver protein were measured....

Waterlow: That has been done.

Fremont-Smith: Well, it ought to answer the question then. Dr Gyorgy was in doubt about what happened to the protein in the liver. What does happen?

Waterlow: The higher the calorie intake, the more the liver protein.

Gyorgy: Who did that?

Waterlow: The experiments were done in Glasgow by Munro & Naismith* (18).

Gyorgy: Did they get fatty liver on the low-protein diet?

Waterlow: No. I think they received choline. They weren't interested in the fat.

Gyorgy: But I would be interested in the fat.

Waterlow: That is a separate problem.

Gyorgy: It is kwashiorkor. That is our problem.

Fremont-Smith: Then the experiment I suggested hasn't been done, and it seems to me that this is, for the purpose of our argument, the crucial experiment; it could absolutely settle this issue as to whether or not liver protein is spared by adding calories to a starvation diet; simply to get the series of rats and then measure total proteins on the livers. The one would be a fatty liver, and the other would be an atrophic non-fatty liver.

Waterlow: I think there is too much emphasis on fatty liver. Later on I am going to present a few results obtained by my colleague, Mr Kean, who has been feeding rats on Jamaican diets, and finds a gross protein depletion of the liver, but no excess of fat.

Gyorgy: And how is their growth?

Waterlow: Very poor.

Gyorgy: Those rats don't have kwashiorkor, I would say.

Waterlow: So is the growth of the child with kwashiorkor very poor.

Gyorgy: No, or not necessarily.

Rao: Dr Waterlow, do you mean that unless the liver is fairly normal in protein, you don't get fatty infiltration? Your observation is that in the growing rat, you get a fatty liver, but not otherwise?

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* On looking up the original paper I find that my interpretation was not strictly correct. Munro had two groups of rats, one on a protein-containing and the other on a protein-free diet. On the protein-containing diet an increase in calorie intake caused an increase in liver protein, whereas on the protein-free diet it caused a *decrease*. This decrease was not great, but was statistically significant. The human cases with which we are concerned usually have some protein intake, however low, and therefore would fall somewhere between Munro & Naismith's two groups. Moreover, the Glasgow workers did not test the effect of very low calorie intakes. Their lowest was [illegible] kg. cal./sq m./day.—J. Waterlow

WATERLOW: No, Kean's rats get something which, to me, is much more interesting—a protein-depleted liver—because I am going to argue that the presence of fat in the kwashiorkor liver is to a large extent irrelevant.

GYORGY: Well, I would be prepared immediately to challenge that comment. (Laughter.)

BRAS: On the morphological evidence of the biopsy alone, I am not always able to differentiate between the liver of the marasmic child and that of the child which shows kwashiorkor clinically.

GYORGY: Why could not a child with kwashiorkor become marasmic?

BRAS: When I say 'marasmus' or 'kwashiorkor', I mean the terms that are applied by the paediatrician to the child at the time of biopsy. As a matter of fact, the difficulty you mention is a real one, because the paediatricians have decided, for convenience of terminology, to use the terms 'kwashiorkor', 'marasmic kwashiorkor' and 'marasmus', indicating three types of the disease. As far as the biopsy goes, in many cases I certainly would not, with any amount of confidence, be able to differentiate sufficiently and say 'this is kwashiorkor'.

DEAN: Dr Bras, do I understand that here in Jamaica you think of a continuing process which has at one end kwashiorkor and at the other end marasmus?

BRAS: I do not think in terms of a continuing process, but of one being an end stage of the other. What I meant was that the clinicians, when they observe a child and when they try to put a label on it, find themselves in difficulties. They cannot always classify it as belonging to either the kwashiorkor or the marasmus group. They have to adopt a subgroup in between, because they claim that they actually see intermediate stages with full-blown kwashiorkor at one end and typical marasmus at the other.

CLEMENTS: Could Dr Stuart help us?

STUART: I think our clinical differentiation is not meant to define the underlying process; it is meant only for working purposes, to determine the clinical condition of the patient. We therefore use those three terms, kwashiorkor, marasmic kwashiorkor and marasmus; in the middle group we think that we see signs of each of the other groups, and that is the reason for the clinical nomenclature.

CRUICKSHANK: It is an artificial situation, but it is practical from the clinical point of view.

CLEMENTS: But is it artificial if it is practical from the clinical point of view? You are dealing with cases, with bodies, showing clinical signs which the clinician cannot separate into two distinct categories; therefore he has to put in the intermediate category, so I think we have to go back to the question raised by Dr Dean. Is it a continuing process? Can anybody answer that question, from a clinical point of view?

Rao: This classification has created the whole confusion. That is how the whole discussion arose in the Gambia. It was really a compromise. We are still not quite sure what is malnutrition or generalized undernutrition, what is kwashiorkor, whether one is the beginning and the other is the end. That is why we again come back and are begging the question once again.

Clements: What are the clinical signs which are specific for the disease? We have no answer.

Cruickshank: The clinician is making his observations, in the first instance at least, from one point in time. Therefore, he can't talk in terms of a continuing process as yet. We are using this classification here, so far, as a name for a process as we see it at a given single point in time. We may have to modify it in the individual case as the process goes on; so that from the practical point of view I think the word, 'continuing', has to come out of the clinical interpretation.

Rao: But unless we define definitely what are the clinical criteria, I think we will have worse confusion. Consider cases in which the clinical appearance is quite specific, say, of marasmus, and then the cases we were shown in the Gambia, which, you remember, always had a swollen face. Well, are they the same? Suppose you get oedema of the face; is the condition more advanced? Those are the questions which are still to be answered.

Clements: But hasn't Professor Cruickshank raised the vital point—again, time? At what stage in the case?

Rao: That is why you must find out whether kwashiorkor is a separate entity or whether it is a continuing process or somewhere in between.

Fremont-Smith: Won't this need prolonged study of individual case histories, with the clinical picture followed through at different times? It seems to me also that this kind of discussion does one very good thing: it makes much clearer to us the vistas of our ignorance.

Williams: I feel that we get a lot of mixed conditions; it is impossible to say in many of the cases whether they belong entirely to one group or another, because the diet and the absorption may vary from day to day.

Clements: That is largely what Professor Rao has said.

Waterlow: May I interrupt?

Cruickshank: I think I am going to speak on your behalf. The point which the clinician wants to make, I think, is that he wants to observe these cases over a long period of time, to see what correlation the biochemist and the clinician can give us during that time with changes in the clinical picture. Dr Waterlow, I think, is going to do that, at least in a small way, with a small number of cases.

WATERLOW: But apart from, or even before that, why I want to interrupt this argument is that I feel this meeting is doing exactly what I said we did in the Gambia—muddling up the planes of thought. I am trying to talk to you about the concept of protein depletion and you keep talking about clinical differentiation. I think they are different things.

RAO: But the clinician is faced with a problem.

WATERLOW: Yes, I know; I don't deny the clinician's problem. But I would like to see if we could get clear about the concept and talk on that level first. Then we can see how to use this concept to help in making the clinical differentiation.

FREMONT-SMITH: You want to talk now about the concept of protein depletion and not about kwashiorkor, and later on, you are going to bring it back to kwashiorkor. But at the moment, you are talking of unclinical, experimental protein depletion; is that right?

WATERLOW: Yes, exactly. If you want, I am talking right up in the air.

RAO: On the theoretical plane.

HILL: As Dr Williams said, all these conditions are mixed. We are talking about kwashiorkor, but the concept of kwashiorkor certainly differs clinically all over the world, and maybe there are other factors in it besides diet, such as, perhaps, toxic factors. There are many different lines of thought leading, possibly, to one fundamental concept that Dr Waterlow is trying to expound: that in the body, by some means or other, there is a protein deficiency. He is starting from that, and he is arguing from a fundamental metabolic change within the body as distinct from all the different methods of producing kwashiorkor in its various clinical manifestations.

WATERLOW: Yes, I have been trying to examine the idea of what a protein-depleted organism is like, and the only point I have made so far was that organs suffer loss of protein, loss of cellular cytoplasm. The next point, then, was the influence of calories on this; looking at it theoretically, I am maintaining that whatever else may happen, the higher calorie intake should protect against the loss of protein. It may also have other deleterious effects, which we can talk about later. Another important effect of a higher calorie intake will be to prolong life under conditions of protein depletion. That seems to me clear from the clinical picture. Babies with marasmus die at a much younger age than those with kwashiorkor. I think that totally starved animals or human beings die not only of protein deficiency, but of total energy deficiency. A higher calorie intake enables them to survive long enough for a severe state of protein depletion to be established. It may be established at a slower rate than in the totally starved organism, but you may end, eventually, with a greater final degree of depletion. Therefore, in considering the state of protein depletion, we have to think of three things: the *degree* of depletion, the *pattern* of depletion and its *chronicity*. Our ultimate aim must be to find some means of assessing these three factors, and seeing how they interact in a given case.

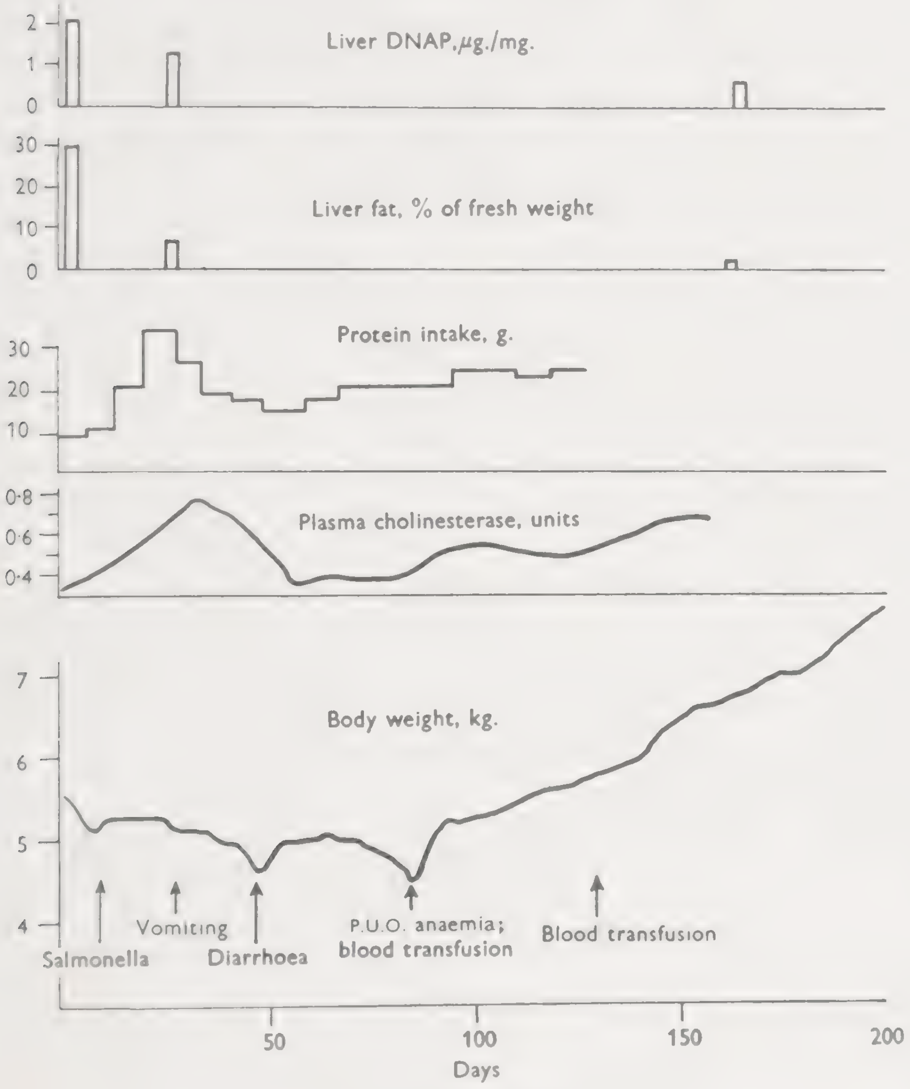
This brings me to the third question that I raised at the beginning, one that seems to me of the utmost urgency: how can we measure the degree of protein depletion of a human being? It is a most paradoxical fact that although most of us think that protein deficiency in the broad sense is probably the commonest deficiency in the world, yet it is the hardest to diagnose except in extreme cases. This brings me on to practical matters; I say that some means of measurement is urgently needed because, although I have been working on this problem in the ward and in the laboratory for 8 years or so, and many malnourished infants have passed through my hands, I am still unable to predict which case is going to do well, or to make any accurate prognosis. Some of the babies die. some recover quickly, some slowly. I have no means of assessing the severity of the malnutrition or of the depletion in each case. In fact, it is as if someone working on the anaemias had to rely on clinical observation alone, without any haematological measurements. Therefore I think that our next objective must be to find some method of measuring the degree of protein depletion. This should be done on cases of all types, regardless of any distinction between kwashiorkor and marasmus, since I believe that they are both protein depleted, though doubtless other influences come in as well. A quantitative measure of the degree of protein depletion would provide a background against which these other influences could be seen in their proper perspective.

The figures that follow illustrate some of the difficulties which we have encountered. Text-fig. 1 shows data from a case of what we would call typical Jamaican kwashiorkor. This was an infant who was fat and 'blubbery', in Jelliffe's phrase, with extreme wasting of the muscles, hypoproteinaemia, oedema, a large liver containing 30% of fat and a low plasma cholinesterase. After a month we did a second biopsy and the liver fat was almost down to normal; the child had lost its oedema and the plasma cholinesterase was well up. At that point I had to go to the United States for 3 weeks and I was quite confident that when I got back the baby would have been discharged. That was in February. It was discharged sometime in June; the figure shows what happened in the interval. The failure to gain weight is not entirely due to diarrhoea, which was not severe. The diarrhoea may account for the slight fall at 50 days, but the body weight remained stationary for nearly 100 days. The plasma cholinesterase fell, for what reason I don't know, and took a long time to go up—and all this, in spite of the nearly normal liver fat at the time of the second biopsy (30 days).

GYORGY: Oh, well, John, now be careful. Normal liver fat? How can you tell what it was between the second and third biopsies?

WATERLOW: All right: objection accepted.

GYORGY: And you have no values in between?



Text-fig. 1. Case 1.

WATERLOW: I would like to be able to plug that gap in my defences but unfortunately I cannot. The second point is that throughout that period of stationary weight the protein intake was not too bad, being in the neighbourhood of 3–5 g. of protein per kilogram of body weight per day. The baby was not suffering from severe vomiting or diarrhoea, yet it took a long time to get out of this stationary phase and for satisfactory weight gain to begin.

RAO: Excuse me, but what diet do you give when the child is having diarrhoea?

WATERLOW: We try various diets. At that time, I was very keen on Dr Dean's banana diet.

GYORGY: The protein you gave was milk protein?

WATERLOW: Yes, skim milk.

GYORGY: All the time?

WATERLOW: Yes.

DEAN: We found it was the sugar that upset the children, including the sugar in the dried milk; this limited the protein we could give in that form.

WATERLOW: I know that; but we have found this diarrhoea very variable. We try to give them bananas or other forms of carbohydrate, such as oatmeal porridge.

DEAN: You keep the intake of protein up, or does it drop as it did here? You say it dropped to under 20 g. a day?

WATERLOW: It dropped to under that at 35 days; then it went up again, and I thought that probably, at about 50 days, I had been pushing it too high.

DEAN: That is not, of course, our conception of what happens; we push in as much protein as possible in a form that does not provide any opportunity for the development of diarrhoea. But as soon as you get diarrhoea the absorption of protein falls.

WATERLOW: I want to emphasize that the diarrhoea was transient and did not extend throughout the whole stationary period.

I am very diffident about my treatment of these cases. I don't think I am good at treating them, and don't wish to argue the pros and cons of different treatments. I merely want to give you a pattern of something that happened.

DEAN: Yes, I understand that. Do you mind my commenting as you go along?

WATERLOW: Oh, no.

DEAN: We got an apparent improvement when we gave a lot of protein, and then we got the development of gastro-intestinal upset and a fall in weight. But after I had treated many cases, I realized that I was not getting very much in the way of weight gains, because my total calorie intake was never really enough. I was concentrating so hard on giving protein that I was quite forgetting that a child of this kind probably needs about 150 calories per kg., that is, twice as much as a normal child would need. As soon as I realized that I was, in fact, producing a case of partial starvation in the child by not giving enough calories and as soon as I found ways of adding more calories, the weight gain of the child improved.

Waterlow: Do you think that this stationary phase might be due to a calorie deficit?

Dean: Yes, that is one possibility. The second point I would mention is that I had children who did not gain in weight, in spite of a large calorie intake, until they were given a very large amount of vitamin B_{12}. The therapeutic diet contained enough B_{12}, I thought, for their needs, although, of course, we know that the amount of B_{12} does depend on the amount of protein in the diet. When I gave a large dose of B_{12} on top of everything else, I was able to bump some of these children out of the stationary phase.

Waterlow: I have never tried that. I have been anxious to get some idea of how they behave without supplements before adding anything to the diet.

Mackay: Does this give you some clue about the action of B_{12}? Would you speculate on it?

Dean: I would rather not, at the moment. I would like to hear what else Dr Waterlow has to say about the enzyme work, which is so closely linked with it.

Fremont-Smith: Did you notice, Dr Waterlow, how calmly we all listened to you, after we had had a chance to pour out the various things we had to say—even though those things were irrelevant and at different levels and quite muddling? Only then were we ready to listen in a calm and peaceful way to what you had to say. I think it has worked out quite nicely.

Waterlow: Well, I'm glad you think so! (Laughter.) Text-fig. 2 shows a case which was stationary for something like 100 days; the liver fat went down at a very early stage from 40% to a normal level, yet the general condition remained very poor. Again, the plasma cholinesterase, which on the whole we have found a most useful measurement, did not bear very much relationship to the general condition, if you judge by body weight. It rose to a normal level fairly early, but the body weight still did not increase for quite a long time. Whether the sudden gain in weight at about 130 days has anything to do with the ventriculin treatment, I don't know. I wouldn't like to say. The point which I would like to emphasize and which these figures are meant to show is the stationary phase. What is happening? Dr Dean has suggested that it may be due to an inadequate calorie intake. I think that is perfectly possible.* It might also be that such a degree of protein depletion has been reached that the condition is semi-irreversible

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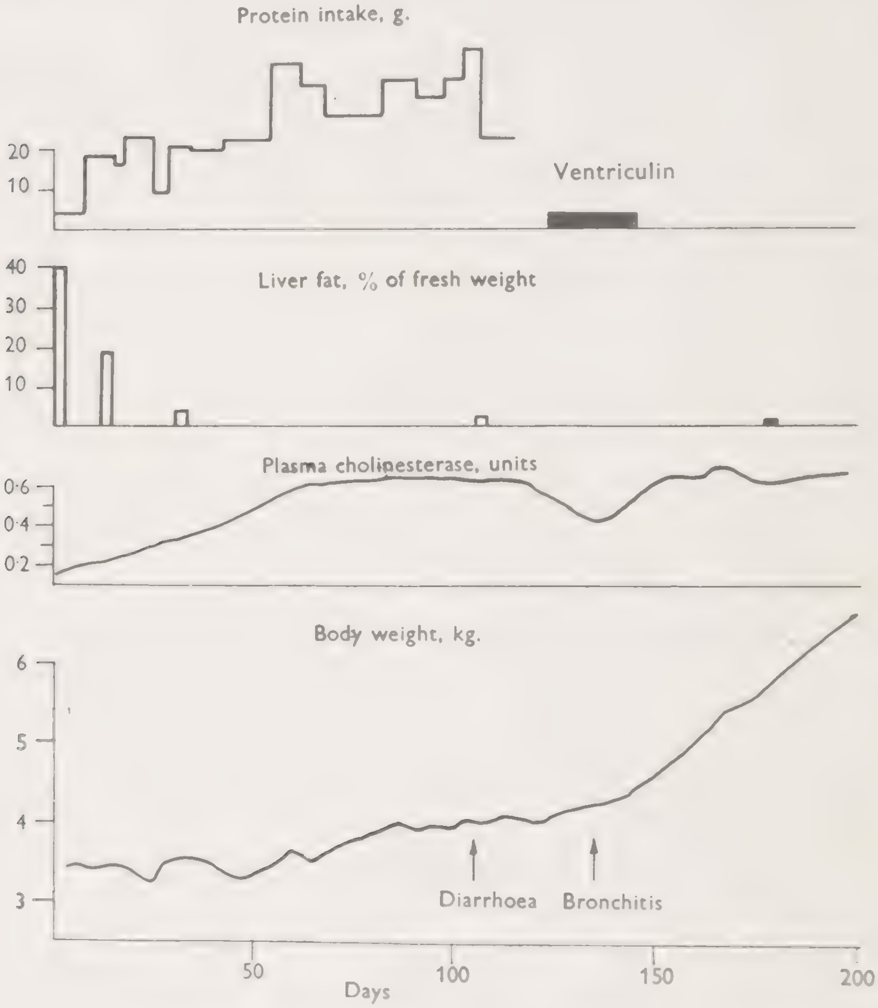
* The calorie intakes of these two cases have since been calculated, and are estimated to have been:

Days ...	0–50	50–100	100–150
Case 1 (Text-fig. 1) Cal./kg.	70	97	94
Case 2 (Text-fig. 2) Cal./kg.	90	112	113

through loss of enzymes for resynthesizing body tissue. I think that is possible, but very difficult to prove.

Gopalan: In our cases of kwashiorkor, we observe the same thing—the weight remaining stationary at a low level for a long time after treatment has been started. We have been intrigued by this phenomenon but do not think it is due to deficient calories, because in our cases we give adequate calories. I am under the impression that the explanation for this stationary phase may be as follows: It is quite possible that although the oedema has disappeared clinically, there may still be an excess of fluid in the extracellular compartment and it may take a long while for this to disappear; we have actually found, in a number of cases of nutritional oedema, that long after the oedema has clinically disappeared the thiocyanate space is still very much raised. So it is quite possible that two things are happening in



Text-fig. 2. Case 2.

these children with almost stationary weight—disappearance of excess fluid bringing down the weight, and an increase of muscle substance causing the weight to go up. But your observation, Dr Dean, about vitamin B_{12} is very interesting.

Dean: I haven't done enough to be certain about it, but I have found a difference in several cases. Dr Waterlow, did these children improve in clinical condition when you started to treat them?

Waterlow: They lost their oedema and fatty liver.

Dean: Our children have this terrible lassitude and anorexia.

Waterlow: Yes, anorexia is a problem.

Dean: If that doesn't disappear in 4 or 5 days, we reckon that our treatment is going wrong, or that we have missed a complication. It seems to us that nearly all the improvement occurs in that short period.

Waterlow: But then why do they remain stationary for so long afterwards?

Dean: I think your treatment was faulty in some way.

Waterlow: I am sure it was, but in what way? I would like to go on to the point that Dr Gopalan raised. One of the ways of attack on the problem of how we can measure the degree of protein depletion of an organism is the classical one of nitrogen balance or nitrogen output. The greater the degree of body depletion, the smaller the nitrogen loss on a nitrogen-low diet, and the greater the nitrogen retention on refeeding. Therefore, we have begun to do measurements of nitrogen balance. I haven't yet enough results to speak with any confidence. We haven't been concentrating on them as much as we should have, and many things go wrong; nor have I been able to do anything with girl babies. In the case shown in Text-fig. 2, at 70 days and again at 90 days, we did balances which I thought were technically satisfactory. These showed retentions of between 2 and 3 g. of nitrogen a day. That child, throughout the stationary phase, had no diarrhoea, and no anorexia; it was retaining nitrogen, and if it had gone on doing so at the same rate for a month, it should have gained 2 kg. in weight, which it did not. Our treatment may have been faulty, but in what way I don't know.

Stuart: May I interrupt for a moment? I think you are mixing up two things, because, in our clinical experience, we find that typical Jamaican kwashiorkor responds very well to treatment within a few days. The cases with which we have trouble are the marasmic ones, not those with typical kwashiorkor, so I think there is something more to it than pure protein deficiency alone. I think Dr Waterlow and I agree that there must be some other element besides the protein deficiency, simply because of the response to treatment, which is so different in the two types of case.

Waterlow: I am not sure that I do agree with that. I think that if we could measure the degree of protein depletion, we might find that the worse the depletion, the longer it took to respond and the more there was a tendency to get into an irreversible state. In case 2 (Text-fig. 2), for instance, if I could go back to the point made by Dr Gopalan, nitrogen was being absorbed and retained in amounts greater than could be accounted for, I think, by experimental error, but body weight was not being gained at an equivalent rate. Therefore, it does seem that there must be a process going on of the kind which he speaks about—a loss of water going hand-in-hand with retention of nitrogen; in other words, there is still an excess of fluid in the body, even after the loss of oedema.

This brings me to the second method which I should like to propose as useful for assessment of the degree of protein depletion: that is, measurement of body composition. I know that Gopalan has data on this, which are very interesting. I have not been doing these measurements for very long, but I have found two cases where, without any clinical oedema, the total body water was 80% of the body weight instead of the normal 55–60%. I measured total body water by the antipyrine method (19); I have not yet tried to differentiate between extracellular and intracellular fluid, because the methods for measuring extracellular fluid are so unreliable, and therefore I do not know where the excess fluid is. If we could measure body specific gravity as well, we would have three independent measurements—weight, specific gravity and total body water, which should give a fairly complete picture of body composition. I am working on a method for measuring body volume, and hence specific gravity, in babies, but this problem is not yet solved. All I can say, therefore, is that we are thinking along this line—the measurement of body composition—and have obtained one or two results which suggest that there may be excessive hydration in the absence of any clinical oedema.

GOPALAN: My observations on body composition pertain mainly to cases of nutritional oedema, and by nutritional oedema we mean a syndrome which is, I think, the result of a combination of calorie and protein deficiency. Although these observations were made mainly on adults, I think they also apply to cases of kwashiorkor.

First, we find that our cases on admission—that is, at the height of the disease—show an absolute diminution of the plasma volume. I mention this because when one goes through the literature on the subject, there is much confusion. Some workers claim that the plasma volume is actually increased, while others say that it is stationary. I think that the importance of this observation, namely diminution of plasma volume, arises when we begin to interpret certain values which we are in the habit of expressing as concentrations. For example, under the influence of treatment you may have a very considerable increase in the amount of circulating plasma protein or haemoglobin, but this improvement can be masked by the concurrent increase in plasma volume. We have had this trouble quite often. We were carrying on some studies on plasma proteins, and were intrigued to find that there was no appreciable increase in concentration, but later on, when we found that there was a parallel rise in the plasma volume, we were able to explain it.

The second thing I want to say is this: with regard to the extracellular fluid volume—the thiocyanate space to be exact—we find that there is an absolute increase (20). There has been some confusion on this aspect also. It has been claimed by certain workers, particularly Dr Keys, that the extracellular fluid volume in starvation states does not absolutely increase but remains constant, while the rest of the tissues shrink, with the result that there is a *relative* increase. But in our cases we find an absolute increase in the extracellular fluid volume at the height of the disease, and, after treatment, there is a diminution of extracellular fluid volume in every case we have investigated.

In our cases, we have found that there are two changes taking place at the end of treatment. We find the extracellular fluid volume decreasing and the total body solids increasing, which is what you would expect (Table 1). But we did not find any correlation between the diminution of the extracellular fluid volume and the increase in total body solids. I say this because there are some authors who maintain that the increase in the extracellular fluid volume which occurs in simple or complicated protein deficiency is a replacement phenomenon, fluid simply replacing the tissues which are lost. If that were so, I should expect that with treatment, the diminution of the extracellular water volume should correspond to the increase in the total body solids. We do not observe that.

Thirdly, we find, at the height of the disease, an increase in the intracellular fluid volume also. The intracellular volume is deduced by subtracting the thiocyanate space from the total body water, and shows a diminution at the end of treatment. This is contrary to what you might normally expect, because, under the influence of treatment, you would expect that the cells would be built up and that the intracellular fluid volume would rise; but, actually, we find that it falls. We interpret this as evidence of excessive intracellular hydration at the height of the disease. I think, therefore, that in cases of nutritional oedema in adults, as well as in kwashiorkor, we are dealing not merely with extracellular oedema but with intracellular oedema also.

These are the more important observations that we have made in our study of body composition.

Table 1. *Body composition in nutritional oedema on admission and after disappearance of clinical oedema*

(From 'Body composition in nutritional oedema', by Gopalan, C., Venkatachalam, P. S. & Svikantia, S. G. (1953). *Metabolism*, **2**, 4, 339. Reproduced by kind permission of the editors of *Metabolism*.)

No.	Time interval between estimations (days)	Grade of oedema	Height (in.)	Body wt. (kg.)	Total body water		Thiocyanate space		Intracellular water		Total body solids		Cellular solids		Minerals		Depot fat		Cellular hydration (%)
					Absolute quantity (l.)	% of body wt.	Absolute quantity (l.)	% of body wt.	Absolute quantity (l.)	% of body wt.	Absolute quantity (kg.)	% of body wt.	Absolute quantity (kg.)	% of body wt.	Absolute quantity (kg.)	% of body wt.	Absolute quantity (kg.)	% of body wt.	
1	46	+	64·5	39·5	34·6	87·6	18·7	47·3	15·9	40·3	4·9	12·4	2·37	6·0	2·50	6·3	0	0	87
		0		42·0	28·8	68·6	17·3	41·1	11·5	27·5	13·2	31·4	5·75	13·7	2·59	6·1	4·87	11·6	67
2	72	+ +	61·5	46·8	42·5	90·8	18·9	40·4	23·6	50·4	4·3	9·2	1·50	3·0	2·74	5·9	0	0	94
		0		45·1	30·1	66·6	13·6	30·1	16·5	36·5	15·0	33·2	8·25	18·3	2·98	6·6	3·78	8·4	67
3	17	+	56·5	42·3	36·6	86·5	20·6	48·7	16·0	37·8	5·7	13·5	3·66	8·7	2·03	4·8	0	0	81
		0		34·1	22·1	64·8	11·1	32·5	11·0	32·3	12·0	35·2	5·50	16·1	2·06	6·1	4·44	13·0	67
4	23	+ + +	59	58·0	45·3	78·1	25·5	44·0	19·8	34·1	12·7	21·9	9·32	16·1	3·36	5·8	0	0	68
		0		50·7	34·9	68·8	13·4	26·4	21·5	42·4	15·8	31·1	10·75	21·2	3·41	6·7	1·64	3·2	67
5	64	+ +	54	44·5	39·0	87·6	24·2	54·5	14·8	33·2	5·5	12·3	3·15	7·0	2·35	5·3	0	0	83
		0		35·5	26·0	73·2	12·4	35·0	13·6	38·2	9·5	27·0	6·7	18·8	2·45	6·9	0·35	1·3	67

Waterlow: Your finding of an 'intracellular oedema' fits in very well with my ideas, but what about the measurement of total intracellular solids? That is the fundamental thing which I am trying to get at as a measure of protein deficiency. Your figures, Dr Gopalan, depend on assumptions whose validity is to some extent open to question, although that could not be helped.

Gopalan: I quite concede that some of the assumptions I have made are assailable. I have made them fully conscious of the possible objections because in fact they are weighted against my final conclusion. For example, I have assumed that body fat at the commencement of treatment is negligible. Doing that, I overestimated the cellular solids. If I have still demonstrated, in spite of this overestimation of cellular solids, that there is excessive intracellular hydration it increases the importance of the observation. Therefore, those assumptions, though they may not be entirely valid, may perhaps actually increase the significance of the conclusions.

Waterlow: You can then demonstrate a decrease in intracellular solids at the time of admission?

Gopalan: Yes, I will put it the other way. There is an increase in total body solids after treatment in all cases investigated.

Mackay: What happens, probably, in protein deficiency is that you have an abnormal cell membrane, and consequently the normal balance of the cations and water across each side of the membrane is destroyed. In severe protein deficiency this is evidenced by diarrhoea, which is one form of fluid loss, and also by pulmonary oedema, changes of blood volume, and so on. It seems to me that what you are seeing in your results is probably evidence of an abnormal cell membrane. Wouldn't it also be reasonable to look into the cations and see what happens to them?

Suppose you have an abnormal cell membrane, say, the lining of the gut; if you could measure the fluid loss to the lumen of the intestine, and the changes in the permeability of the cell membrane, you might be able to show something. It might help if we put forward the idea that in protein deficiency we simply have abnormal cell membranes and that is the cause of these changes.

Gopalan: I was just trying to present some observations without attempting any explanation of the mechanics involved. It is likely that the increased hydration is the result of changes in the cell membrane.

Mackay: What is the ionic exchange picture, do you know?

Waterlow: We have very little information.

Mackay: I think that is one of the features that might be worth thinking about.

Dean: There is a point to be made here. We were working in Germany on cases of what I think must be considered pure hunger oedema, without any element of protein malnutrition—if Dr Rao will excuse my making that distinction—and we found an increase in the extracellular fluid. Of course, we were aware of the suggestion that there might be some damage to the cell membrane, but we could find nothing to support that. We now think there are other things which are probably responsible for these curious shifts in body water.

Fremont-Smith: In what respect could you find nothing to support it? You made a very general statement there. What kind of evidence did you have that went against there being a change in cellular membrane?

Dean: All the investigations we made of such things as the minerals in the plasma were completely normal. These were only mild cases of hunger oedema, but they had a very considerable alteration in water partition. We couldn't find any alteration of the kind you might expect.

Gyorgy: It is possible to have normal potassium values in the plasma, but still low potassium in the cells.

Dean: Yes. We did not do the therapeutic potassium test, and we found nothing in the electrocardiogram. But you know what a complicated thing it is to try to establish definitely where potassium is.

Gyorgy: That means you still have no evidence about intracellular changes.

McCulloch: Did you have any ascitic fluid, to do any tests on that?

Dean: No. We never found ascites in a single case of hunger oedema.

Gopalan: The question has been raised as to the actual mechanism underlying this retention of fluid. That was your point, wasn't it, Dr Mackay?

Mackay: Yes.

Gopalan: The observations which we have made of an increase of antidiuretic substance will partly explain this accumulation of fluid. They will not explain the accumulation in any one particular compartment.

Clements: Is it physically possible to get intracellular hydration without some movement of electrolytes?

Mackay: It is possible. If you have a loss of extracellular electrolyte, then you can get intracellular hydration. It need not necessarily involve a migration of electrolytes across the cell membrane. This occurs in miner's cramp.

Waterlow: I learned a great deal from Dr Darrow on this subject in Havana; it was clear from what he told us that the extracellular electrolyte pattern, particularly for potassium, tells you practically nothing about intracellular changes. The only way to find out whether the cell mass is depleted of potassium is by balance studies—to see if the child retains more than it should. If one is measuring nitrogen balance, it would be perfectly possible at the same time to measure mineral balance.

If there are no more comments, I would like to summarize quickly what

I have said so far. Dr Gyorgy has suggested that I was oversimplifying in trying to make out that there is no difference between kwashiorkor and marasmus. That is not what I meant. Undoubtedly, there is a distinction, and I myself have written about it and tried to define it on several occasions (6, 21). Perhaps I could explain my point best by the analogy I gave before with the anaemias. No one would dispute the clinical difference between an Addisonian anaemia and a hookworm anaemia; but in order to understand the nature of this difference it is necessary to have measurements —of cell count, cell volume, haemoglobin, etc. —as a quantitative basis for comparing and contrasting cases, whether of the same or of different clinical types. I have been led, then, to suggest that what we would like to know in kwashiorkor, marasmus and all intermediate states, is the amount of protein in the body or, in relation to the normal, the degree of protein depletion of the body. It seems to me an urgent task to try and put this on a quantitative basis. The chain of events has therefore been that clinical observation led to the concept of protein malnutrition, and this concept has indicated the next line of investigation.

Then I suggested three ways of tackling this problem, two of which we have already dealt with—measurement of nitrogen balance and of body composition. Now we come to the third—measurements made on individual organs, such as blood, pancreas and liver. Those differ from the first two, in that they will never give a picture of what is happening in the body as a whole. But they may give us very useful evidence of variations in the pattern of depletion.

Now I know that there are many people who have valuable data on changes in the blood, in pancreatic secretions, etc. I intend myself to speak only about the liver, on which I have been working for several years. I have now come to the conclusion that this was a mistake, of the kind which Gillman so well described as 'too narrow a concentration on a single organ'. For a time my thinking was dominated by the fatty liver, which made a great impression on me when I first worked in the West Indies. But it was going too fast to try and find a single metabolic lesion which would explain the condition. It would have been better to concentrate on simple straightforward measurements, as of nitrogen balance. The work I have been doing on liver enzymes is no doubt something that in the end has to be done, since there is plenty of experimental evidence that they may alter in malnutrition (20), and presumably these alterations have some meaning. But from the immediate practical point of view I don't think this is the best way of tackling the cases with which we are faced.

For this reason, and because many of the results have already been reported ([illegible]), I shall not say much about the liver enzymes. In the last year, in keeping with the line of thought that I have been trying to develop, we have been working more and more on the simple composition of the liver as a possible guide to the composition of the rest of the body. For many years we have been measuring the fat content (which is easy) and, more recently, protein and nucleic acids; Dr Patrick has now begun to do measurements of glycogen, so that gradually we are able to form quite a comprehensive picture of the gross constituents of the liver. It is about these that I want to speak now.

First of all, consider the fat. Fatty liver is very common here; out of thirty-eight cases of malnutrition that I have recently summarized, fifteen had a liver fat content of more than 30%, and eight had a fat content of more than 40% of the fresh weight. These are very large amounts, even compared with the fatty livers produced experimentally.

In 1945, when I first worked on this subject in Jamaica, I concluded that the severity of the disease and the prognosis depended on the amount of fat in the liver. I now think that is wrong. The experience I have had of measuring the fat content, both here and in Africa, has not helped me much to decide how bad the case is or what is going to happen to it. Of these eight infants with 40% or more of fat in the liver, only three died. Some of those with less fat in the liver also died. There is, as far as I can see, no clear-cut correlation between the degree of fatty infiltration and the likelihood of death. The reason for this is, I think, that there are other things happening in the liver besides fatty change.

Pl. 1 shows a typical section of a fatty liver. The enormous fat vacuoles are surrounded by a thin rim of cytoplasm—so thin that it is like a membrane which, in many places, is ruptured. The appearance is rather like that of the fatty cysts or 'lipodiastemata' of Hartroft (26) but I don't want to use the term, because Dr Bras tells me they are not quite the same. These broken cell walls may be partly artefact, but like most histological artefacts I believe they have their significance; that is to say, they wouldn't break if they weren't so fragile.

The thing that stands out in such a liver is not only the enormous amount of fat, but also the very small amount of cytoplasm. Platt used to talk about the 'lean and hungry cell'—the cell of the liver which had lost 40% of its weight. This might be called the 'fat and hungry cell', if one can coin such a phrase.

I think that two things are going on in these livers: they have accumulated a lot of fat and, like the starved liver, they have lost a lot of cytoplasm. If, as my experience suggests, the amount of fat is not closely related to the general condition of the patient, one asks oneself: 'perhaps the other factor is the relevant one—the amount of loss of cytoplasm?'

Thus in the liver we have two processes—increase of fat, and loss of cytoplasm—both of which may be present in varying degree, and which, as regards the size of the liver, work in opposite directions. This idea would explain the very great variability in liver weight and size that we get in these babies. Again, if one could accept the argument that fat does not matter very much, then a non-fatty marasmic liver, which has lost a large proportion of cytoplasm, is comparable to a fatty liver which has lost an equal amount.

I put these forward not as proven facts, but as ideas which are guiding our work. Table 2 shows data on the composition of the liver in four recent fatal cases. The results are rather variable because the cases were chosen at random—the last four livers that we have analysed. These babies were between 8 months and 1 year old. The livers are all larger than normal, and contain 40–50% of fat. In two of the livers the total protein nitrogen is reduced to about half the normal amount. In the first case, however, there was no loss of protein. This is quite interesting, because this child was getting better when it died, not from malnutrition but from Salmonella infection. We don't have so many fatal cases that it is easy to accumulate a large series, but figures such as these confirm the idea of a gross reduction in liver cytoplasm, or liver protein—at least in some cases.

RAO: These are post-mortem tissues?

WATERLOW: Yes. Although these livers are very big, if the excess fat is deducted, it can be seen that they are more or less normal in size.

RAO: It is always best to compare liver weight in relation to body weight, isn't it? In experimental animals, as you know, we always do this and also estimate the fat and water content.

WATERLOW: Yes, but that is difficult. Should we use the ideal or the actual body weight? Since these babies are grossly underweight, the relative liver weight, after allowing for excess fat, would not be too low.

HILL: If I understand correctly, you have the liver weight; then you measure fat and protein. If you add the fat and protein together and subtract them from the liver weight, what constitutes the difference?

WATERLOW: The difference is water and glycogen, I think.

RAO: Do you know the water content of these livers?

WATERLOW: Yes, it seems to be raised.

HILL: Can you tell us what the histological picture is? Are these cells distended with fat?

WATERLOW: Yes.

HILL: If so, where is the water load?

WATERLOW: The water is in the cytoplasm, I suppose.

HILL: But could it be, in a cell like that, which is already distended with fat?

WATERLOW: I suppose it must be, because it can't be in the fat.

RAO: In the experimental rat, the water content of the liver is greater when there is a hepatic necrosis rather than a fatty change.

Table 2. *Composition of liver in four fatal cases of malnutrition*

A. Absolute values in grams

Name (1)	Liver wt. (2)	Total liver fat (3)	Total liver protein (4)	Expected liver protein* (5)
M. Green	650	250	37	40
D. Thompson	480	195	18·5	37
L. Emmanuel	505	260	27	32
C. Allen	430	210	17·5	37

B. Values as percentage of fresh weight

Name (1)	Water (6)	Fat (7)	Non-fat solids (8)	Protein (9)	Ratio of water to non-fat solids (10)
M. Green	48·4	38·4	13·0	5·7	3·7
D. Thompson	48·6	40·5	10·9	3·8	4·4
L. Emmanuel	37·7	51·1	11·2	5·4	3·4
C. Allen	41·8	48·8	9·4	4·1	4·4
'Normal'	70	5	25	18	2·8

* Calculated from the liver weight of the normal infant of the same age. Protein taken as 18 % of liver weight.

WATERLOW: I don't want to lay too much stress on my figures for water content.† There is also a large part of the dry weight unaccounted for as either fat or protein. I have assumed this to be mainly glycogen, but have no direct measurements.‡ These uncertainties, however, about the percentage composition do not affect the figures for total liver protein. I think that the large reduction in the second and fourth cases (Table 2) is significant, and I hope to prove this further from the biopsy data.

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† The livers were stored in the deep-freeze before analysis, and the water content may have altered. This would make the figures for percentage composition unreliable, but would not affect the figures for absolute fat and protein content.

‡ The normal liver is composed of about 70 % water, 5 % lipoid, and 25 % of non-fat solids, of which some 18 % is protein; the remaining 7 % includes the nucleic acids, minerals and glycogen, and amounts to about 30 % of the fat-free dry matter. In the fatty livers obtained at post-mortem an average composition would be: 44 % water, 45 % fat, 11 % non-fat solids, of which 5 % is protein, and 6 % is not accounted for. This last fraction, therefore, amounts to more than 50 % of the fat-free dry matter, and so is relatively, though not absolutely, much higher than in the normal liver. I have assumed that it consists mainly of glycogen.—J. Waterlow.

Hill: What about the blood content of these livers? Would that come into your protein estimation?

Waterlow: I think the fatty liver contains very little blood.

Mackay: What is the meaning and significance of the fat deposit in the liver?

Gyorgy: Nobody knows. My personal assumption is that it is an indication of cellular damage in the liver on a low protein diet, because you have simultaneous fat deposition in the proximal convoluted tubules of the kidneys.

Waterlow: On the other hand, I have been trying to maintain that the fat, as it were, doesn't matter. I know this is a thing on which Professor Gyorgy does not agree. But it is incredible how quickly the fat can go. A liver containing 40 % of excess fat may be almost clear in 2 or 3 weeks.

I would like to return now to the question of decrease in total protein nitrogen of the liver. We see the same sort of thing in some rats that my colleague Mr Kean has been feeding on Jamaican diets of yam and banana. These rat livers, which were not fatty, contained only about 10 % of protein (Table 3). This is very low compared with the normal figure of 20 % or more in litter-mates fed a stock diet.

Table 3. *Composition of livers of rats fed Jamaican diets*

(Kean's data.)

Diet	Liver wt. (g.)	Liver protein percentage of fresh wt.	Liver fat percentage of fresh wt.
Jamaican	3·6	9·7	5·3
Stock	9·6	21·9	3·4

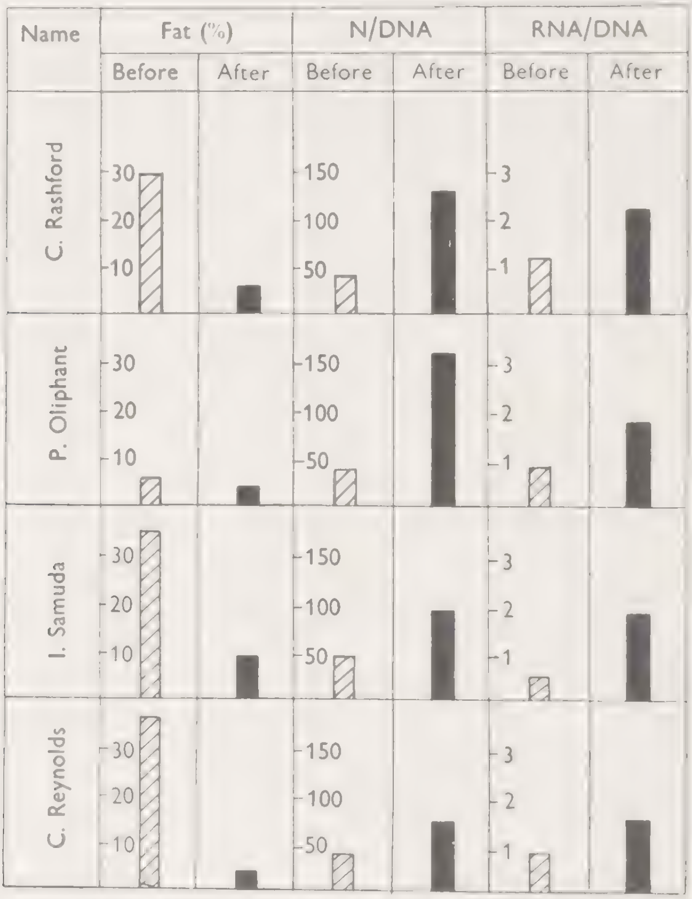
Gyorgy: Normal with respect to what?

Waterlow: The usual figure for liver protein in rats fed a stock diet is about 18 %.

Gyorgy: Yes, that's right.

Waterlow: In these rat livers, protein accounted for only about 30 % of the dry weight. I can't tell you at the moment what makes up the difference in dry matter, because Kean's and my experiments have not gone so far. I think it is glycogen; histologically there is a great deal of glycogen, but we have not measured it chemically. These are two pointers which suggest a decrease in protein nitrogen content of the liver, with possibly an increase in water content.

I wish to end by giving you some of the data from biopsies, which point in the same direction. I need not dilate on the dangers of drawing conclusions from such minute bits of tissue, weighing only 2–3 mg. The first problem is the basis of representation. We would really like to know the total protein content of the liver in relation to body weight, as Dr Rao suggested, but I know of no means of measuring the total volume or weight of the liver *in vivo*. We have agreed that the malnourished liver shrinks and loses cytoplasm, although 'shrinks' is perhaps a misnomer, because it may at the same time be distended with fat. The question arose whether in such a liver it is the number of cells that is reduced, or the size of each cell. All the experimental work that bears on this problem suggests that the number of cells remains unchanged, but that each cell, on the average, becomes smaller [illegible]. As it is well established that the amount of nuclear deoxyribonucleic acid (DNA) per cell is constant (47, 48), we can use the DNA, or DNA phosphorus, as a basis of reference. You will readily see that if the total cytoplasmic protein decreases in the liver in the malnourished state, but the DNA remains the same, then the ratio of protein nitrogen to DNA will be decreased in the malnourished liver. Text-fig. 3 shows the



Text-fig. 3. Fat, RNA and nitrogen in liver biopsy specimens of four cases before and after treatment results of measurements made on biopsy specimens from four cases before and after treatment. In three of the cases the liver was initially fatty, and in all four the ratio nitrogen DNA almost doubled after treatment. That suggests that initially the protein content of these livers was greatly reduced, exactly as would be expected from the animal experiments.

Again, as is well known, ribonucleic acid (RNA) is supposed to be associated with protein synthesis; it is quite interesting, therefore, to know what is happening to that. Text-fig. 3 shows that RNA, in relation to DNA, is low in the malnourished liver, and rises on treatment.

I will admit that these examples shown in the figure are four selected cases, and that every case does not behave in this way. There is a good deal of scatter in the results, which derives partly from the fact that the liver is not a simple tissue; moreover, it tends to be infiltrated with lymphocytes and other cells. Nevertheless, these figures, I think, do give a true picture. In Table 4, I have averaged all the results obtained so far, from twelve cases in all. The DNA per unit weight is high before treatment, as would be expected if the nuclei remain unchanged, and the rest of the liver shrinks. When DNA is used as the standard of reference, both protein N and RNA are much lower in the first specimen than in the second. All these results are significant at the usual level (*P* between 0·01 and 0·05).

Table 4. *Protein and nucleic acid content of the liver in malnourished infants*

(Measurements on biopsy specimens. Means of twelve cases.)

	DNAP, μg. per mg. fat-free dry wt.	Protein N, μg. per μg. DNAP	RNAP, μg. per μg. DNAP
Before treatment	1·73	49·7	1·05
After treatment	1·15	80·3	1·59
Significance of difference, *P*	< 0·05 > 0·01	0·01	0·01

I had hoped that this measurement of nitrogen in relation to nucleic acid in the liver might give me the answer I want—some means of assessing the degree of protein depletion of the individual case. In a way it does, but I can't say that this ratio is consistently lower in fatal cases. It seems to be lower in fatty livers than in cases of marasmus, as Dr Gyorgy will be pleased to hear. But the variability, both of the material itself and that arising from the analytical method, is such that I cannot yet use this ratio as a simple means of assessing severity from a single measurement. I only hope to persuade you that these figures do show a very considerable degree of protein depletion; how far that extends to the rest of the body will be a matter for argument and experiment.

HILL: You did say, Dr Waterlow, though, something about shrinkage. Do I take it that before treatment, histologically, these cells are shrunk?

WATERLOW: They would be, if it were not for the fat.

HILL: You could get the same results by measuring nuclear volume in relation to cell volume.

WATERLOW: Well, these figures for DNA in relation to dry weight give you exactly the same thing in chemical terms. That means that there are more nuclei and therefore more cells per unit volume.

GYORGY: I would like to know what would be the ratio of protein nitrogen to DNA in a child after acute fasting, say, with only 3 or 4 days of acute diarrhoea. I ask the question because I listened to Kosterlitz a few weeks ago at the Macy Liver Conference and, if I am not mistaken, my recollection is that he finds a sudden drop after a very few days—and then the figure stays put; it does not fall further. Therefore, it would not be an indication of chronic protein deficiency, but it could be an indication of an acute protein deficiency.

WATERLOW: Yes, I think that may well be so. My reading of the experimental work is that in 4 days the liver of a rat loses 40% of its weight, and after 7 days the loss is still 40%, because in the intervening period the drain has fallen mainly on the muscles.

GYORGY: You don't have any figures in acute studies?

WATERLOW: No. I would gladly do this on any biopsies provided.

GYORGY: Well, you must have acute diarrhoea in children.

WATERLOW: Yes, we have. We will look into this.

PATRICK: Is the basic assumption, that the amount of DNA is a measure of the number of cells, accepted generally? The reason why I ask is that I have seen one reference which said that in vitamin B_{12} deficiency the amount of DNA went down (29).

WATERLOW: I think it is generally accepted, except in the liver. There you have the difficulty of polyploidy. Moreover, Dr Bras tells me that in my cases—I am talking particularly of fatty livers—as they recover there tends to be an infiltration of lymphocytes. That source of error would minimize the differences I get; that is to say, if there were no cellular infiltration, these differences would be even bigger, and therefore I do not think it destroys my argument, but it does increase the variability from case to case.*

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* These points perhaps need some clarification. The validity of using DNA as a standard of reference for comparing the composition of the liver before and after treatment depends on two assumptions: (1) that the DNA per cell does not change; (2) that the number of cells does not change.

(1) The liver contains many polyploid cells with two or four times the normal number of chromosomes, and so with two or four times the normal amount of DNA. Thus in the rat, according to Davidson and his colleagues (17) the average amount of DNA per nucleus is

My work on enzymes, as I said before, has not given very illuminating results, and I do not propose to say much about it, except this: you will notice that ribonucleic acid is reduced in these livers (Table 4). RNA is associated with the mitochondria and the microsomes, the particles in the cells on which so many of the oxidative enzyme systems are distributed. One cannot help thinking that this reduction must to some extent disrupt the mechanism of the cell; it is, in a way, very extraordinary that so many of the enzymes that we have measured, such as the dehydrogenases and transaminase, should be unaffected by this 'lean and hungry' state of the cell (24, 25). Even an enzyme such as the DPN—cytochrome-*c*-reductase, which is an essential link between the dehydrogenases and the cytochrome system, and which is located on the microsomes, is not reduced, according to the measurements we have made. That is rather surprising, because this enzyme is a flavoprotein, and in these babies with fatty liver there is quite often clinical evidence of riboflavin deficiency.

In recent months I have been particularly interested in the succinoxidase system, which is a chain of several enzymes. I want to throw out the idea—since I believe it is a function of this meeting to pool ideas—that perhaps we should not think too much in terms of *amounts* of enzymes but in terms of their *organization*; possibly the organization of the enzyme systems on the submicroscopic particles might be disrupted, so that they can't work properly *in vivo*, even though *in vitro* you cannot find any change in amount. I am hoping that I may be able to produce some evidence of this, but it is too soon as yet.

The point on which I want to end is that we have not got very far towards discovering the subtle biochemical lesions or changes going on in these cells, and I feel that at the moment the problem of body composition is the one to which we should perhaps give priority.

PATRICK: I want to throw out a rather general suggestion, for work which might be done, which is probably even more theoretical and impractical than many of the things we have discussed as yet. I was wondering if we could get at the fundamental problem of measuring the protein depletion

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9×10^{-12} g. in the liver, compared with $6{\cdot}5 \times 10^{-12}$ g. in the kidneys and other organs. This would not affect the validity of our comparison, provided that the degree of polyploidy—in other words, the average amount of DNA per nucleus—does not change during treatment. Histological observations suggest that if anything polyploidy becomes more marked as a result of treatment; this would tend to increase the amount of DNA per unit weight of tissue.

(2) Infiltrating cells such as lymphocytes mostly contain less cytoplasm than liver cells. Thus a cellular infiltration will also tend to increase the amount of DNA per unit weight of tissue.

Cellular infiltration, like polyploidy, seems to be more marked after treatment. Therefore both these factors, by increasing the DNA content per unit weight in the specimen taken after treatment, will tend to obscure the difference between the first and second specimens. The differences that have been found are therefore all the more significant.—J. Waterlow.

of a person by the use of radioactive isotopes, to measure protein turnover in the body as a whole, or in the liver, using liver slices.

GYORGY: It's a good idea.

DEAN: It would, of course, be one way of getting at the amount of protein depletion in the body, to analyse the bodies of children who have died, wouldn't it?

WATERLOW: Yes.

DEAN: Don't you think that is a practicable thing which should be done?

WATERLOW: McCance did some, didn't he?

DEAN: Not cases of kwashiorkor.

WATERLOW: Isn't it a much more difficult thing than one would think?

DEAN: No, it is not difficult, if you can get the whole body which, in some circumstances, I know is impossible. It seems to me that this would give you a measure of something that you are trying to get at by much more difficult methods.

WATERLOW: Of course, we do have some deaths, but we don't expect the babies to die. I agree that one can learn something from post-mortem material, but it will not help us to plot the progress of the case.

DEAN: Some of these children die after they have been treated, and some die in the acute state, don't they?

WATERLOW: Yes.

DEAN: That might well account for some of your discrepancies in results, mightn't it?

WATERLOW: Yes.

DEAN: I think that something could be done by analysis of the total body, or even by analysis of the total liver for depletion. But I think that nitrogen balances won't help you very much to define what happens because of the peculiarities of absorption and utilization. I have actually done a certain number of balances on children in acute kwashiorkor and again after treatment; they show that in the acute stage the child is unable to absorb very much, but I don't think they tell you a very great deal more.

WATERLOW: But wouldn't the degree of nitrogen retention during treatment give you some idea of the need? It certainly does in animals.

DEAN: It doesn't in this condition, however, in my experience.

WATERLOW: Because of the failure of absorption?

DEAN: Yes. You see, a child has to be in very strong nitrogen balance, doesn't it, to get on at all? Leaving, for the moment, the question of whether it remains stationary or is putting on weight, what we have found is that there was not the expected difference in the child at the beginning and at the end of a course of treatment. I have great faith in the use of nitrogen balance for a particular purpose, but I think you must realize that you get only a limited amount of information from it.

GOPALAN: While we are on the subject of liver changes in malnutrition, perhaps I might make reference to a functional change in the liver which may be of some significance. The work I wish to describe started from a clinical observation.

Table 5. *Urinary output in twenty-six unselected cases of nutritional oedema before treatment*

Urinary output in 24 hr. (c.c.)	No. of cases
Below 200	5
Between 200 and 300	4
Between 300 and 600	4
Between 600 and 1000	4
Between 1000 and 1500	4
Above 1500	5
Approximate fluid intake in all cases, 2000	

Table 6. *Urinary response to administration of 1150 c.c. water*

Output in normal subjects (c.c.)		Output in cases of nutritional oedema (c.c.)		
Recumbent	Erect	Grade of oedema	Recumbent	Erect
1905 (166 %)	1110 (92 %)	+ + +	61 (5·3 %)	18 (1·6 %)
1712 (149 %)	1015 (83·3 %)	+	1120 (97 %)	453 (30 %)
1660 (144 %)	908 (78·7 %)	+ +	1455 (126 %)	20 (18 %)
1765 (154 %)	—	+	1230 (107 %)	338 (29 %)
1508 (132 %)	—	+ + +	440 (38 %)	30 (26 %)

$$\frac{\text{Urine volume in erect posture}}{\text{Urine volume in recum. posture}} = 55\text{–}60\,\%\text{ in normals, }7\text{–}40\,\%\text{ in cases of nutritional oedema.}$$

In cases of nutritional oedema in children, the most striking thing with regard to the urinary output is the pronounced oliguria. In Table 5 I have indicated a 24-hour urinary output in a few consecutive cases of nutritional oedema. Out of twenty-six cases there are only five who had a 24-hour output which could be described as normal. I mention this because when one goes through the literature published in Europe and America, one gets the impression that in this condition the striking feature, as far as urinary output is concerned, is polyuria. I want to emphasize that in our material the striking feature is the pronounced oliguria. This has a bearing on what I would like to say presently.

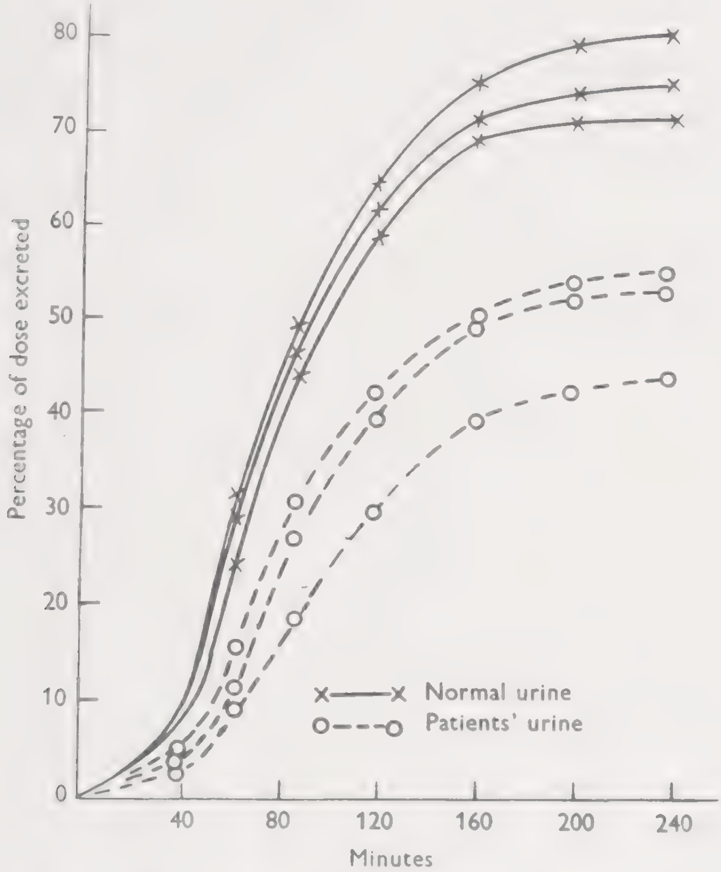
In a few cases of this condition, we have tried to do what we call a urinary output test (Table 6). The test consisted of the administration of a known volume of water on an empty stomach, and then studying the urinary response for the succeeding 4 hours or so. We did this test in two postures, that is, with the patients recumbent and erect, and we also had normal controls on whom we did the same thing. We find that normal subjects excrete over 100% of the ingested fluid in less than 4 hours if they are recumbent. If they are erect, the excretion is somewhat less. Therefore, even in normal subjects there seems to be some postural difference in urinary response to a test load of water.

There has been some discussion about the mechanism underlying this postural difference, and I think the work of Dr McCance and others has shown that it is possibly mediated through an increased secretion of the antidiuretic hormone of the posterior pituitary in the erect posture (30). When we come to cases of malnutrition, we find that the excretion of urine in both postures is very much diminished; but what is very interesting is that the secretion in the erect posture is a very much smaller fraction of the recumbent excretion than in the normal subject; in other words, the postural difference seems to be exaggerated in cases of nutritional oedema. It would appear that, whatever the factor which is responsible for the postural difference in normal subjects, it is present in increased amounts or, perhaps, it operates with increased intensity in cases of nutritional oedema.

In a few cases of nutritional oedema we tried to collect the 24-hour urinary output and to assay the antidiuretic potency of the urines (Fig. 4). I won't go into the actual details beyond stating that we employed the classical method of Burn (31), using hydrated rats as our assay animals. The interrupted lines represent the response in cases of nutritional oedema, and the solid lines the response obtained in normal subjects; we find that rats injected with urine of patients suffering from nutritional oedema excrete only 40–50% of the ingested fluid in 4 hours, while rats injected with normal urines excrete over 70–80%. It would therefore appear that the urine of these cases of nutritional oedema contains some antidiuretic substance in increased amounts.

I don't want to claim too much for these observations. An increase of antidiuretic substance in the urine has been reported in such diverse clinical states as premenstrual oedema, eclampsia, and so on, so it becomes difficult to assess the significance of this observation. I think the most important question is whether this antidiuretic substance is purely incidental, being the result of oedema, or whether it has any aetiological significance.

One familiar line of reasoning would be this: we know that the antidiuretic hormone of the posterior pituitary is normally inactivated by the liver. In conditions where the liver itself is damaged, it is possible that the ability of the organ to inactivate the hormone may be interfered with, and therefore there may be an increase in the antidiuretic substance. It seemed worth while to investigate this aspect. We wanted to find out whether protein depletion would damage the liver in such a way as to interfere with its ability to inactivate the hormone.

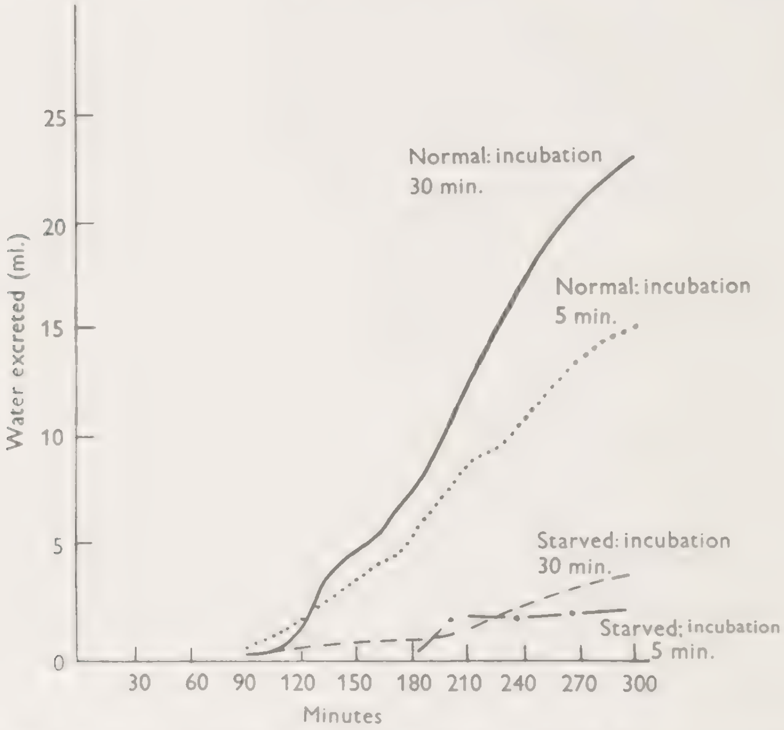


Text-fig. 4. Antidiuretic potency of urine from normal subjects and from cases of nutritional oedema. Assay on rats, by the method of Burn (31).

We incubated pitressin with homogenates of livers of animals which were starved for some time, and also with homogenates of livers from normal animals. The pitressin was incubated for varying times—5 and 30 minutes—and then we assayed the antidiuretic potency of the two samples (Text-fig. 5); we found that the pitressin incubated with starved liver homogenates exercised a much greater antidiuretic effect than pitressin incubated with normal liver; it would appear that the liver is so damaged in starvation that its ability to inactivate the antidiuretic hormone is greatly reduced.

Next, we tried to see if we could get the same findings with animals which were put on a low protein diet, because that would be more applicable to cases of kwashiorkor, and we did get a similar finding there also (Text-fig. 6).

I wish to repeat that I do not want to claim too much for these figures, but it seems to me, when we begin to examine the numerous hypotheses which have been put forth to explain the pathogenesis of nutritional oedema, that the hormonal factors have been ignored. Most of these hypotheses begin and end with physicochemical factors, which are of course important; but we know now that the hormonal factors, particularly the posterior pituitary and adrenal cortex, play a very important role. All I want to point out is that any hypothesis which seeks to explain the pathogenesis of nutritional oedema and which ignores the hormonal aspects is incomplete.



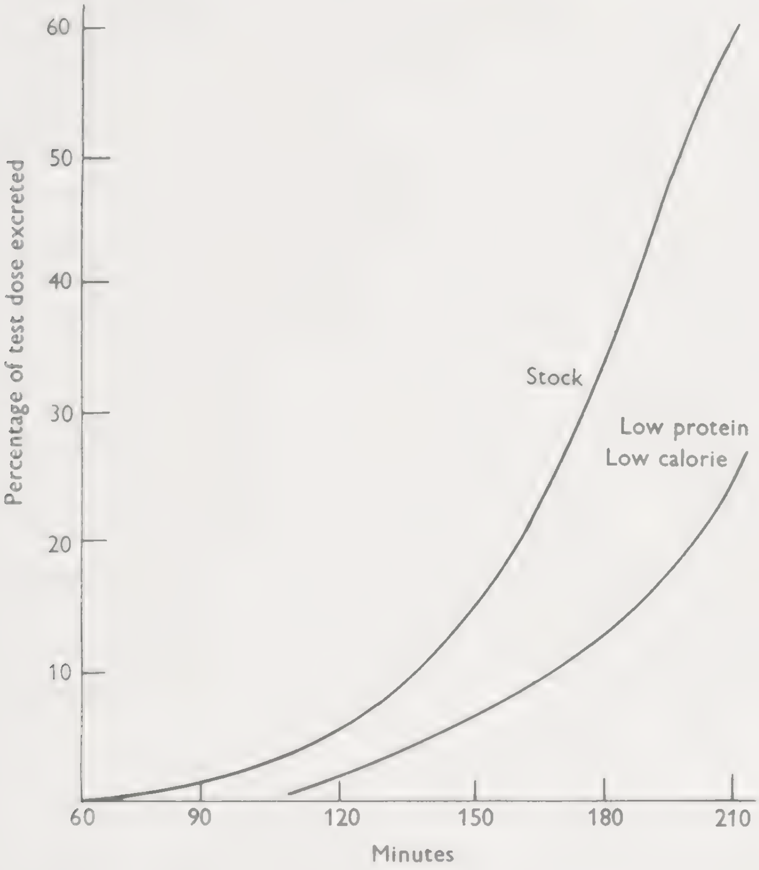
Text-fig. 5. Antidiuretic potency of pitressin after incubation for 5 or 30 minutes with homogenates of liver from normal or starved rats. Water excretion after a test load

I know that these observations are controversial, but it is for this very reason that I put them before this meeting. (Applause.)

Dean: It might interest you to know that two pieces of work have been done in Kampala along these particular lines. The first was a repetition of the rat experiments, done slightly differently, which brought out the same point. The rats were given the local diet of banana until they reached a standstill point in growth, and then tests were done on excretion, with a load of water calculated according to body weight. That is one of the techniques, as you know, for doing this kind of assay. The other thing, on which Professor Heller of Bristol has recently been working in Kampala, is his own modification of this assay using jugular vein blood. You probably know of that, Professor Gyorgy. I think he reported part of it in Canada.

Gyorgy: Yes, in Montreal (32).

Dean: He found that in the acute stage of kwashiorkor there appeared to be a larger amount of antidiuretic hormone or something like that—he is very cautious about what he calls it—circulating in the blood of these children; after treatment the amount went down. Heller says you must not conclude from this that the liver is damaged and that the trouble is all in the liver. He is quite sure, I believe, that destruction of the antidiuretic hormone occurs in other organs, including the kidney. I mention this only because here are similar observations on cases of kwashiorkor, and I think, Dr Gopalan, yours were cases of adult nutritional oedema, weren't they?



Text-fig. 6. Inactivation of pitressin by liver homogenates of rats fed on stock diet and on low protein low calorie diet.

Gopalan: Yes.

Dean: But the two findings fit very well together.

Williams: I think that all the guests of the Japanese will sympathize very much with these findings. I would like to point out that polyuria doesn't wait for nutritional oedema to develop, and that the postural factor is very important; in fact for prisoners of war it became extremely important functionally in the social life of the camp, so much so that someone wrote a poem:

> How doth the little internee
> To eat her rice delight!
> She guzzles what she gets by day
> And liquidates all night.

FREMONT-SMITH: I would like to raise a couple of points. I thought Dr Gopalan's was extremely beautiful work. As Dr Dean pointed out, one of the problems is, to what extent are his findings representative of oedematous conditions in general, and to what extent characteristic of his particular group of cases, that is to say hunger oedema.

In this connexion, I should like to refer to the work of Ralli at New York University(33), and also to the series of papers by Ephraim Shorr and his colleagues at Cornell(34), and to speak of the difference in the recumbent and erect postures. I believe there is evidence to show that the normal individual in the erect position relatively promptly loses fluid from the plasma by capillary filtration into the lower limbs, and this is one of the factors that affects the diuresis in that position; in oedematous conditions and also in subclinical oedematous condition, the outpouring of fluid under hydrostatic pressure or in the erect position is very much more rapid. This is more or less related to the results of the old McClure-Aldrich salt wheal test, in which the wheal disappears very much more rapidly in the presence of oedema. This was shown to be due to mechanical distension of the tissue spaces by the preceding oedema, so that the wheal which is produced in the skin just pours out into the already distended tissue spaces. My guess is that part of the difference in your patients with oedema, as compared to the normal, in the recumbent and in the erect position, is the increased outpouring of filtered fluid from the plasma into the lower limbs.

Lastly, I would like to refer to some work of my own, a very small number of cases tested in 1929 for their capacity to produce a normal water diuresis. I took a group of various kinds of oedema—cardiac, nephritic, nephrosis with oedema, and one case of cirrhosis of the liver with oedema—and was able to show that in all these there was delay in water output after a test load. The output was also delayed in eclampsia, and even more strikingly in normal individuals given typhoid vaccine or malaria, during the rising-temperature phase, until the fever had reached its peak.

The charts of these patients looked for all the world as though you had given them a dose of pitressin or pituitrin; they showed the same delayed diuresis. In all three instances, in the various types of oedema, in the patients with a rising temperature, and in individuals who had been given pitressin, if you gave them water to drink, they not only had a delayed diuresis but also a very sharp dilution of the blood; freezing-point depression, total protein and electrolyte concentrations decreased, indicating quite a severe dilution of the blood, which the same individuals did not show in response to a test load of water when they were normal. I thought that this, perhaps, bore indirectly on your work and that reference ought to be made to it.

Mackay: I would like to ask Dr Waterlow whether he has any information on the diet of his children with fatty liver.

Waterlow: Only the histories that we get in the ward.

Mackay: I was leading to the simple question, how do you explain the accumulation of fat in the liver?

Waterlow: I can't explain it. I don't know what causes the fat. I have been trying to find out for a long time.

Mackay: You haven't a dietary history which would make possible some guess regarding factors in the diet?

Waterlow: The dietary history is usually the same—of a baby which has been abandoned or whose mother has gone out to work; or the baby developed an infection, and for that reason was taken off the breast and fed on sugar-water and cornmeal porridge. My dietary histories are not sufficiently detailed for us to make an accurate calculation of the actual intake. I think Dr Rhodes has much better data.

Rhodes: I have done some dietary inquiries and measurements in the homes of cases with kwashiorkor, because I was interested in their intake of protein and total calories. Usually there was a history of sudden onset of anorexia 2–4 weeks before admission to hospital, and from that time the diet was very low indeed, in some cases consisting only of bush tea and sugar. Such cases present with oedema, muscle wasting, and obvious recent loss of a large amount of subcutaneous fat. The history of the diet before anorexia had set in at first led me to believe that there had been a *high* carbohydrate and low protein intake. A child was often fed six times a day, receiving at each feed porridge with sugar and milk and, perhaps, sweetened bush tea in the morning. I then tried to measure the quantities of food from particulars obtained from the mothers, and I invariably found that the caloric intake, as well as the protein intake, had been exceedingly low and the intake of animal protein practically nil. These children received a minimum of condensed milk, which constituted their only source of animal protein, and one carbohydrate food, such as cornmeal, in quantities insufficient to supply them with the calories needed. My impression was that every one of the twenty-three cases of kwashiorkor I investigated had a diet deficient in both protein and total calories.

Table 7 is an example of a diet which a child with kwashiorkor received before the onset of anorexia. This child was 1 year old and weighed, on admission to hospital, 11·7 lb., including oedema fluid. The oedema was severe and the actual body weight therefore was less than that. She had six meals per day, four of cornmeal porridge with sugar and condensed milk. That, I think, gives one the impression of a high carbohydrate diet. In the table are given measurements of the daily quantities of this diet, which show that the calorie intake was in fact low.

Table 7. *Average daily diet of child with fatty liver disease, aged 1 year, weighing 11·7 lb.*

MENU

6 a.m.	Bush (mint) tea with brown sugar and condensed milk
8 a.m.	Cornmeal porridge with brown sugar and condensed milk
11 a.m.	Cornmeal porridge with brown sugar and condensed milk
1 p.m.	Cornmeal porridge with brown sugar and condensed milk
3 p.m.	Cornmeal porridge with brown sugar and condensed milk
7 p.m.	Mint tea with brown sugar

MEASUREMENT

Type of food	Amount (g.)	Protein (g.)	Calories
Cornmeal	42	4	144
Brown sugar	60	0	240
Condensed milk	45	3·7	141·5
Total	172	7·7	525·5
Requirement for age	—	33·0	1000

GYORGY: I have to interrupt you. I'm sorry, but your conclusion is not borne out by the facts. This child weighs 11·7 lb., or 5 kg., with oedema fluid. Therefore, its intake, on the calorimetric basis, should be about 500 cal.; its actual intake was therefore perfectly satisfactory.

RHODES: But this was the diet that the child was on 3 weeks before admission to hospital. During these 3 weeks, according to the history, it had nothing but sweetened bush tea in very small quantities.

CLEMENTS: When was the weight of 11 lb. taken?

RHODES: When the child was admitted to hospital with gross oedema. When she was at home, on the diet shown in Table 7, I think she must have weighed more than 11 lb., because on admission there was clinical evidence of recent weight loss.

CLEMENTS: Even if its weight at home was 14 lb., it wouldn't be grossly undercaloried at 500 cal., would it?

GYORGY: I would say no.

Rhodes: I think it all depends on whether you take the actual weight or the ideal weight.

Mackay: Isn't the point of confusion that Dr Rhodes is using age instead of weight?

Gyorgy: That is correct. On the weight basis, this child had enough calories.

Mackay: It is not only the weight of the moment. You have to consider that the child has to increase its weight. It has to make up some leeway so that its calorie requirements may really be higher than those specified from standard tables for a particular weight.

Clements: Yes, I agree with that.

Mackay: So I wonder if Dr Rhodes is not correct in her assessment.

Fremont-Smith: For what purpose do you need the calories; for maintenance of weight or regaining weight?

Gyorgy: You need calories both to cover energy expended, and also for growth.

Fremont-Smith: Can the issue be stated in this way: suppose two children weigh the same amount, 11 lb., one of them having reached that point in the normal course of development, and the other one having lost 8 lb. If 500 cal. were adequate for maintenance of weight—let's just talk of maintenance and not of regaining—by the child who had grown normally, would the same calories be adequate for maintenance by the one who had shrunk? I think that is the issue.

Clements: I don't think that is what happened. The usual story is that they reach a certain weight and then maintain a plateau, or that they put on weight very slowly.

Gyorgy: Rubner & Heubner (35) and later a large number of physiologists and paediatricians have recommended for practical purposes the so-called energy quotient as index of calorie requirement. This is the ratio of total calories as contained in the daily diet to body weight in kilograms. According to the Rubner law, the calorie requirement is determined by the surface area. Surface area is closely related to weight, according to special formulae. Therefore weight is really the indicator for calorie requirement. 100 cal. in young infants per kg. body weight and 70 cal. at the end of the first year should cover all calorie requirement, including growth. In marasmus, the active protoplasmic mass is higher than in well-nourished infants with large fat depots. However, the difference in total calorie requirement is not significantly different between a normal (eutrophic) and atrophic infant. But calories *per se* will not help the undernourished child to put on weight and grow. The need is for protein and other essential nutrients of which the body has been depleted.

Dean: I don't think the intake in Dr Rhodes's case can be satisfactory, because if that child continues to receive 525 cal., it is going to die.

Gyorgy: Not because its calorie need was not covered, but probably on account of the poor diet and the far advanced protein-depletion of vital tissues. We might say that the child could be near death, because essential tissue enzymes have reached a very low level. If this child were to get only calories in the form of carbohydrate, you would probably accelerate its death.

Clements: The outstanding thing is that the calorie intake is not grossly deficient, but its protein intake is.

Aykroyd: The amount of sugar in that child's diet was most remarkable. I have never seen anything like that before anywhere else in the world.

Waterlow: Yes, a 'sugar baby'.

Williams: Very often these children do not get the cornmeal properly cooked, so that the amount of calories they get is not what it should be from values in the tables. The cornmeal is also providing all the protein that the child is having.

Gyorgy: Yes, this should be emphasized. Not a low calorie intake, but the low protein intake and the poor quality of the protein is the leading aetiological factor in kwashiorkor.

Sénécal: In Dakar, when we look at the pathogenesis of kwashiorkor, we find that there is a low protein intake, but a normal or high intake of carbohydrate. The first sign that we see in kwashiorkor is diarrhoea, and I feel that this is due in many cases to the predominantly carbohydrate diet.

McCulloch: Could Dr Rhodes tell us how she got those figures of consumption?

Rhodes: Yes; I went to the mother's house and I said, 'What do you give your baby and what utensils do you use? Give me the exact food.' I had a pair of small scales, and anything she told me or gave me, I measured and weighed on the spot. The figures may be rather high, because, in my experience, the mothers tell you that they give more, rather than less, than they really do.

McCulloch: The point I make is that your calorie evaluation is probably more or less correct, but even the 7·7 g. of protein that you have is probably an overstatement, judging by our experience round Port Antonio.

Scrimshaw: As a point of future reference when we refer to the characteristics of the kwashiorkor syndrome in Central America, the figures for the diet in certain cases there are remarkably similar to those Dr Rhodes showed. For example, Autret & Behar ([illegible]) describe four cases from Sumpango, a town in the Guatemalan highlands in which kwashiorkor is common. The nutritionist found a 7-year-old girl consuming no more than

261 cal. and 6 g. of protein, of which only 1·5 g. was of animal origin. This is not of course the usual diet of this child, but the one which immediately preceded her appearance at the clinic with kwashiorkor.

CLEMENTS: You said 7 years; don't you mean 7 months?

SCRIMSHAW: No, I mean 7 years.

GYORGY: What was the weight?

SCRIMSHAW: Unfortunately the weights are not available. Another child, a boy 2 years of age, was receiving, immediately prior to his visit to the clinic with kwashiorkor, 265 cal. and 5 g. of protein, of which less than half a gram was of animal origin. Another similar child, a girl 3 years of age, was found to be consuming 244 cal., 2 g. of animal protein and 10·0 g. of total protein. The last one of this set, a boy of 26 months, was a little better off—519 total calories, 9 g. animal protein, and 18 g. total protein in his diet immediately before he was seen in a rural clinic with the disease.

AUTRET: Dr Scrimshaw is referring to children seen by Dr Behar and myself during our survey of Central America. Those children were fed a very low diet, because they had intestinal troubles, but we do not know how long they had been on this low diet.

CLEMENTS: I wonder if they are the same as Dr Rhodes's case, because these cases of Dr Scrimshaw's are obviously grossly undercaloried, and you would expect chronic malnutrition of the worst kind. In Dr Rhodes's case, are we getting a true protein deficiency in the presence of something approaching adequate calorie intake? I think that is the whole point at issue here.

SCRIMSHAW: From other studies we know that the usual diets of the children I mentioned were reasonably adequate in calories but grossly deficient in good quality protein. These particular children were thrown into their acute kwashiorkor, however, by a diet which represents almost a starvation regime.

DEAN: I think Dr Rhodes's and Dr Scrimshaw's figures are most valuable in showing just what these children are taking. We know from the fact that they were admitted to hospital that their calorie intake had certain results. I think that is the value of Dr Rhodes's investigations.

CLEMENTS: Do we know that? I think it is an assumption. Do we know that that diet had certain results, or was there some other factor? After all, we must not forget the point made by Dr Fremont-Smith earlier, namely, that there may be a multifactorial cause of a situation. Did this child suddenly get an intercurrent infection? Did it suddenly become grossly disturbed by a parasitic infestation? Are we right, then, if we don't know these things, in assuming that it is the diet that brought the child into hospital, if the child had been going along on this fairly monotonous diet for 4 or 5 months? Then, as in Dr Rhodes's case, something happens, anorexia develops, and it is precipitated into hospital. Why should this be?

WATERLOW: I have seen many reports which suggest that the onset of kwashiorkor is precipitated by an infection. In Brazil, for instance, several clinicians said this to me. Would you not agree, Dr Santos?

SANTOS: Yes.

CLEMENTS: The child should have reserves, but it has nothing on which to draw.

MACKAY: Is there any evidence by which we can explain, in these human children, the production of fatty livers on the basis of dietary factors?

WATERLOW: The question of calorie intake in relation to fatty liver is a point which has been discussed many times. Until we get some accurate dietary surveys, which are difficult, I feel that we are talking theoretically. Dr Scrimshaw has given us some figures, and I know that Dr Gopalan has some too, but we don't know much about liver fat in these cases. In time we shall get enough figures, to prove the point—is a relative excess* of carbohydrate in the diet a factor in causing the fatty liver, as one would expect from the experimental work (37)?

SCRIMSHAW: It seems to me that we are going to come back again and again to the problem of whether the requirements of the child with kwashiorkor are principally determined by its requirements for maintenance or for maintenance plus growth. When it comes to the problem of which amino acids are limiting, are we going to apply the results of the studies of amino-acid requirements for maintenance, or for growth? The child is not growing; yet he is trying to grow.†

VAN DER SAR: May I ask Dr Rhodes if she observed any difference in the time at which fatty liver developed in relation to the duration of the breast feeding? Suppose a child had been breast-fed for 4 months, and weaned thereafter, how many weeks would elapse before it gets a fatty liver? If it were breast-fed for 8 months, how long would it then take before a fatty liver developed? Does it make any difference?

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* A relative excess in relation to protein and vitamins.

† Brock & Autret (38) concluded that methionine was deficient in the diets of children with kwashiorkor in Africa, and others have stressed the widespread deficiency of methionine in diets of persons in underdeveloped areas. This is certainly true if the methionine requirement of these children is almost 30 % greater than the lysine requirement and more than four times that for tryptophane, as Rose finds for adult maintenance (39). If the growing child, however, is similar to the growing rat or dog or pig or chick in its amino-acid requirements, nearly twice as much lysine is required as methionine and the tryptophane requirement is about one-third that for methionine. The requirements estimated by Albanese for the male infant (40) agree with those latter ratios. It should also be remembered that for adult maintenance most of the methionine can be replaced by cystine, and in vegetable diets the amounts of cystine are usually as great as those of methionine. Even in the growing animal some of the methionine can be replaced by cystine and there is no reason to believe that the human child is an exception. For these reasons the question posed in the discussion must be faced and answered in at least a tentative fashion before we can use dietary survey results to help evaluate the role of specific amino-acid deficiency in 'protein deficiency disease'.—N. S. Scrimshaw.

RHODES: This question of breast feeding in Jamaica is a little complicated. Most of the cases which I saw were either not breast-fed at all or partially breast-fed from the age of 2 to 3 months—and 'partially' means two or three times during the night and not at all during the day. Therefore, these cases had not been fully breast-fed for a considerable period. Complete weaning usually takes place between the age of 7 months and 1 year or more. But the main point is that complete breast feeding is discontinued at 2–3 months, when supplementary feeding starts. I can't say that I have seen any direct relationship between stopping of breast feeding and the development of fatty livers.

VAN DER SAR: I would like to ask the amino-acid content of the mother's milk. There must be some difference in mother's milk in the different parts of the world.

GYORGY: Apparently not; to my knowledge, there is no difference in the protein content.

CLEMENTS: The only work I am aware of is that by Auffret & Tanguy in Dakar (41), and it needs confirmation. These two workers analysed samples of milk from coloured women living in Dakar for methionine. They found that the methionine content of the whole milk proteins in three samples of pooled human milk was 1·28%. This is low compared with the figure of 2·3–2·4% found by Block & Bolling (42) in the milk proteins of both white and coloured women in the U.S.A.

Dr Mackay asked about the dietary history in babies with fatty liver, in the hope, I take it, of getting some clue to the cause, and to why these cases differ from those of marasmus. We are all agreed that the protein intake in kwashiorkor is very low, and Dr Rhodes has put forward the view that there is also a calorie deficit. This, however, seems to be controversial, and without more data we cannot pursue the question further. There is also the problem of what precipitates the onset of kwashiorkor. This we could take up again on the clinical day. We might, now, return to the point where Dr Waterlow left off—the attempt to define biochemical processes and changes characteristic of the malnourished organism.

DEAN: We have tried to find ways in which we could make a diagnosis of kwashiorkor in biochemical terms. For this we have used children, who as far as we can tell have been free from any complication, and were not subject to anything like a sudden bout of diarrhoea or other infectious condition that might have affected not only their biochemical composition, but also the liver. Isn't it a fact that if you have an infection, fat is liable to be deposited in the liver, but in a different place from where it is found in kwashiorkor? At least, that is what Davies tells me, and there is no doubt that in a number of infectious conditions you do get fat in the liver, although the child cannot possibly be suspected of having kwashiorkor; so what we have tried to do is to find a group of children who were completely free, as far as we could tell, from any combination of kwashiorkor with some other disease.

I should like to ask whether any other people have had biochemical experience of a group of children of that kind, and to find out whether we could come to some kind of agreement about what are the useful methods of diagnosis—the biochemical methods that can be used in such children. I think, as long as we do not have anything that is related definitely and objectively to a condition which is fairly pure, we cannot possibly hope to distinguish between marasmus and marasmic kwashiorkor and kwashiorkor.

We may be able to do so if we can find the right set of biochemical diagnostic criteria. I am therefore going to mention the combination of biochemical investigations that, in our experience, seems to distinguish the pure case of kwashiorkor as we see it. You must remember that my experience with kwashiorkor is limited entirely to one small part of Uganda and to a group of about 150 cases that have been under my charge, of whom about forty satisfied my criteria for uncomplicated kwashiorkor. My figures are related to those children, and are not necessarily related to cases in other places. We have published these criteria several times (43), and I think they are more or less established. The child with kwashiorkor has been on a low protein diet and shows evidence of failure in growth; he may have changes in the hair and in the skin (but we don't think those are absolutely essential) and, in the acute condition, anorexia, misery and lassitude; he has oedema and dies unless he receives the proper kind of treatment. There is usually a fatty liver, and there is usually a change in the pancreas, but, as Dr Waterlow has said, the lability of the fat in the liver is so extraordinary that I am not surprised if a typical case does not have any fat at the time you happen to examine it. It seems to be quite likely that the fat may disappear in a short time. I have defined these criteria much more carefully and better in a paper I wrote with Schwartz on the biochemistry of the uncomplicated condition (44) but, on thinking about it now, I have three suggestions. The first is that the total serum protein seems to be a valuable criterion. I used to think that the fractionation of albumin and globulin was diagnostic, but I am not too sure about that now.

Waterlow: But we do see reduced serum proteins in cases that are clinically diagnosed as marasmus.

Dean: Yes, that's all right. If I may go on through this list of things.

then tell me, when we have them all together, if they make something complete.

In these children we also find a low blood urea, which at one time I thought was diagnostic, but I am quite sure now that the blood urea in a child is labile; if you feed a child on a low protein diet, it is likely to have a low blood urea. There is also a low total cholesterol, down to about 50 or 60 mg. per 100 ml. of serum, and a very high ratio of free to esterified cholesterol.

GYORGY: The cholesterol is low in marasmus and starvation as well.

DEAN: And is the blood urea low also?

GYORGY: No.

DEAN: We also find that there is a fairly low, but not very low, alkaline phosphatase; the non-specific esterase, which is measured by the splitting of phenyl benzoate, is low, and the blood amylase is low.

The esterified form of cholesterol is produced, of course, by cholesterol esterase acting in reverse; so there we have a series of enzymes that are affected, and rather peculiarly affected. Alkaline phosphatase, for instance, goes down at first and then goes up during treatment, and we have now come to the conclusion that our method for estimating alkaline phosphatase was, in effect, estimating not one but more than one alkaline phosphatase. We have started working on the fractionation of alkaline phosphatases according to their activation by magnesium and their inhibition by cyanide. I think there are no less than three, which probably have their origin in different parts of the body.

The non-specific esterase is also a thing which may be produced in more than one part of the body. We might get some useful information if we were to try again this method of fractionation of enzymes which, as you know, you do by estimations at different pH levels.

I have not mentioned cholinesterase because I worked with cholinesterase some time ago and thought that it had something to do with undernutrition in Germany. I then found that it was liable to be affected by all kinds of conditions, and I discarded it. If a child is ill with almost any disease, the cholinesterase goes down, and when it gets better, the cholinesterase goes up. But this combination of a low total protein, a low cholesterol with an alteration in the ratio of free to total cholesterol, and the peculiarities of the phosphatase, esterase and amylase, is one which, to my mind, is difficult to find in any state except kwashiorkor.

I have a conception of kwashiorkor as a generalized enzyme defect, occurring not only in one organ of the body but in many organs, and I am not particularly interested in any one organ. Therefore, I agree wholeheartedly with Dr Waterlow when he says that too much emphasis, perhaps, has been placed on the liver. It is only one of the parts affected. I think

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that if we are to investigate kwashiorkor in an academic manner, the right thing to do is to go for the possibility of a generalized effect which shows up in every cell.

I have tried to get people to bite on the idea that it is the thiol enzymes which are most affected. Then I found that Dr Waterlow, 6 months before, had mentioned it at one of the Macy conferences. Did you get any further with that idea?

WATERLOW: No, not much further yet. The trouble is that with every new enzyme it takes me 6 months to perfect the methods of assay.

DEAN: Yes, I know it is a difficult job.

RHODES: Dr Dean, when you say that generally the cholinesterase goes down when the child is ill and comes up again when it gets better, are you talking of any child?

DEAN: Yes, a normal child which has an infective illness has a lowered cholinesterase.

WATERLOW: Nevertheless, we find, in general, that it is a useful clinical index of severity and progress. Don't you find that?

DEAN: I don't think so. It is down in the acute state and it is up when the child gets better, but there seem to be so many things that can cause that kind of alteration that I am trying to find something which is rather more specific.

WATERLOW: Admittedly the changes are not completely specific, as you can see from the figures I showed (Text-figs. 1 and 2).

DEAN: Yes, when the child got diarrhoea I noticed that the cholinesterase went down. That might have nothing much to do with kwashiorkor, if my idea of some fault in treatment is correct.

RAO: Dr Dean, you gave your biochemical findings in a group of forty children with kwashiorkor; do you have any comparable group of, say, forty children of the same economic class but without the symptoms?

DEAN: I haven't got forty of them, Dr Rao. I wish I had. But by very careful selection from children of the same age, in the same economic class, and, as far as we could tell, of exactly the same conditions of home life, we were able to find that these things I have mentioned were, I think, specific for kwashiorkor. The one thing which is not specific is the reduced serum protein, which can occur in many conditions.

I would only suggest that the combination of those things that I have mentioned might, as a working hypothesis, be considered specific for the diagnosis of kwashiorkor in biochemical terms. I realize that I am sticking my neck out by doing this, but I wanted, if possible, to get people's ideas as to whether this is a good or bad way of looking at the diagnosis of kwashiorkor.

Rao: It is quite likely to provoke discussion, but have you any comparable group, say, a group of undernourished children?

Dean: No, I have not got that.

Gyorgy: Starvation?

Dean: No. As I said, I have only got children with kwashiorkor.

Rao: Therefore, do you think you are right in saying that these are criteria by which we can diagnose kwashiorkor?

Dean: But I want you or somebody else to take these tests and apply them to your case of kwashiorkor and to your case which is not kwashiorkor but malnutrition.

Rao: It is better to do it in the same area.

Dean: I cannot get these cases of marasmus, you see. I have looked for them but cannot find them.

Hill: In Jamaica we find that the manifestations of protein deficiency vary with different circumstances. How do you know you have an uncomplicated kwashiorkor? You are postulating a human experimental animal, as Dr Gyorgy, for example, would do with his rats. How do you know that they haven't got some superimposed infection or parasite? After all, these are very common in the tropics.

Dean: I made as many investigations as I could. I didn't wish to burden you with the details. At the moment I would just like to say that we have done as much as we could to make sure that we were dealing with the uncomplicated condition.

Scrimshaw: That is the whole point. It must be demonstrated that the chemical changes are not primarily due to co-existing conditions which may or may not be associated with kwashiorkor elsewhere.

Autret: There is one point which should be clarified: what is a normal child in an area where kwashiorkor is prevalent? Dr Dean tells us what should be the biochemical diagnosis of acute kwashiorkor. But was not the diagnosis made from the very beginning by clinically selecting children who underwent the biochemical investigation? Are all the biochemical criteria given by Dr Dean necessary for the diagnosis of kwashiorkor? For example, I found that in the 'normal' child, or let us say, the 'average child' in a poor area of Tonquin, the average figure for the ratio of cholesterol esters to cholesterol was reduced in more than 60% of the population.

Dean: By how much?

Autret: From the normal figure of 75% down to 50%.

Dean: We get much bigger reductions in our cases of kwashiorkor

Autret: Your cases are acute cases of protein malnutrition. The figure I gave is an average figure for what you might call 'normal children' — the average children living in the poor normal conditions of their country.

Dean: Do you think they have mild kwashiorkor?

Autret: I am not saying that, although they surely are to some extent deprived of protein foods, but they go to school, play, and yet show these reduced figures. Much lower figures will be found in mild kwashiorkor, reaching step by step the very low figures you found in acute cases. Thus, some of the biochemical investigations will help to confirm a severe protein deficiency but will not help us very much to diagnose the 'intermediate' case.

Dean: I might mention that in all my cases I did the investigations at intervals of 7 days throughout the treatment of the child. I do not claim that, when I have treated the child for 4 weeks, it is a normal child. That seems to me unjustifiable.

Scrimshaw: Dr Dean has listed a number of chemical changes which he observes occurring in characteristic cases. Individually, any one of those things can happen as a result of other causes. The question then is: does the occurrence of all these things taken together serve as a useful guide to the clinician in diagnosing kwashiorkor? The lowered average values of three of these, total protein, cholesterol and alkaline phosphatase, in non-kwashiorkor cases in our region is well known.

In Central America we find a tendency for the total protein values to be normal or even slightly elevated in cases in which the diet contains protein of predominantly vegetable origin, until the condition becomes quite severe. A sharp fall then occurs (45). But total protein is not an early indicator, unless values slightly higher than 'normal' can be taken as such.

We haven't done sufficient cholesterol examinations in children or in cases of kwashiorkor, but in adults consuming the common diets of the region we find total cholesterol values which are about two-thirds those of the United States standard. These cholesterol values tend to be low at least in the adult population in an endemic kwashiorkor area (46).

Our concept is that if you have a disease which varies from predominantly undernutrition to predominantly protein deficiency, with a continuous spectrum in between, you have any number of factors which may enter and influence it—secondary vitamin deficiencies of different types, infestations and acute infections and chronic disease. The exact nature of the biochemical findings in a region will depend, therefore, not only on the basic characteristics of the disease, but also on the effect of prevailing secondary factors.

This principle is illustrated by Table 8 which shows average serum vitamin A, carotene, riboflavin, ascorbic acid, alkaline phosphatase and vitamin E values for normal school children in Central America. The levels for ascorbic acid are remarkably high by any standards. Group averages between 1 and 2 mg./100 ml. are common and some groups average more than 2 mg./100 ml. Riboflavin values are within the normal range. Vitamin A and carotene levels are either within the lower limits of normal or abnormally low, depending on the criteria used. Alkaline phosphatase values are also in the low normal range.

Table 8. *Blood serum values in Central American school children*

N	Constituents of blood serum	Mean	S.D.
712	Riboflavin (μg./100 ml.)	1·57	1·02
661	Vitamin C (mg./100 ml.)	1·57	0·88
633	Vitamin A (μg./100 ml.)	25·5	9·7
712	Carotene (μg./100 ml.)	84·0	47·0
696	Vitamin E (mg./100 ml.)	0·65	0·26
699	Alkaline phosphatase (mM./l./hr.)*	5·04	1·83

* 1 Millimolar unit = 1·79 Bodansky units approx.

In Table 9 appear values for cases of severe malnutrition in Costa Rican infants. The blood values for both riboflavin and ascorbic acid are still within the normal range, although in severe malnutrition and particularly in kwashiorkor, in some parts of the world, the riboflavin values would be low and the ascorbic acid values might approach zero. The nutrients which are low in these cases of severe malnutrition are the same ones observed to be low in the school children, i.e. vitamin A and carotene. Alkaline phosphatase, already somewhat low in the school children, is also still lower in the cases of malnutrition. I would appreciate your comments on this. What does it mean?*

GYORGY: You omitted to discuss vitamin E on both tables.

SCRIMSHAW: I don't know what it means. Do you?

GYORGY: It is exceedingly low, the lowest figure I have ever seen—0·08 mg./100 ml. I am very much impressed by the difference between the two groups in Table 9.

SCRIMSHAW: This is the second condition in which we have found vitamin E paralleling vitamin A and carotene. The other is in the incidence of false positive serology (47). Whether or not it goes with a lowered lipoprotein fraction in the blood, we don't know, but that seems a reasonable possibility. In our opinion it is a secondary phenomenon rather than a primary one.

CLEMENTS: What do you mean by 'acrocyanosis'?

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* A short article has since appeared (48) supporting the thesis that the alkaline phosphatase determination measures the activity of several enzymes arising from different sources. The larger portion is believed to be variable, responding quickly to fasting and largely derived from the intestine. This could readily explain the lowered values in kwashiorkor and the response to therapy.

Peña Chavarria: We mean by 'acrocyanosis' a peculiar colour of the extremities—the feet and hands, and sometimes even of the nose and ears, which we see in many cases of severe malnutrition.

Clements: Is it clinically distinguishable from pink disease or is it a different condition?

Peña Chavarria: By pink disease you mean acrodynia?

Clements: Yes.

Peña Chavarria: In many cases, I think it is just the same, because we see the pink colour, and the peeling, and the perspiration, and the mental and psychotic changes.

Table 9. *Infant malnutrition in Costa Rica*

Serum component	Malnutrition with acrocyanosis	Malnutrition without acrocyanosis
Protein (g./100 ml.)	4·31	4·85
Free Riboflavin (μg./100 ml.)	1·61	1·86
Vitamin C (mg./100 ml.)	0·66	0·92
Vitamin A (μg./100 ml.)	16·8	17·2
Carotene (μg./100 ml.)	19	22
Vitamin E (mg./100 ml.)	0·57	0·08
Alkaline phosphatase (mM./l./hr.)*	2·16	1·79

* 1 Millimolar unit = 1·79 Bodansky units approx.

Scrimshaw: This confusion is probably my fault, because I balked at the term 'acrodynia' for these cases. I didn't believe that they were true acrodynia. This term 'acrocyanosis', which did not commit us, was a compromise.

Peña Chavarria: For that reason we don't want to call it 'acrodynia'. We are very timid in that respect. Perhaps acrodynia is pathogenically related to this condition; as you know, it has been suggested that acrodynia may have a nutritional basis. For that reason we began to investigate the biochemistry of cases of malnutrition with and without acrocyanosis.

Hill: Are these lesions pink or are they bluish?

Peña Chavarria: Some of them are pink, some are bluish.

Williams: I used sometimes, to see cases on the Gold Coast which reminded me very much of pink disease, but we never got the complete picture with photophobia. In kwashiorkor I did not see any sign of acrocyanosis. But one thing that always struck me, from the earliest days, was the coldness of the extremities; that, I found, was always an important and serious clinical sign. When I first got these cases, we had 80 % deaths. But when radiant heat treatment was used, the mortality rate was less

HILL: In this connexion, it is perhaps worth mentioning that we are investigating tropical ulcer, which we think may have a nutritional basis. I was first put on to this by a classical case of kwashiorkor, which, incidentally, had a cirrhotic pancreas; when we examined the skin of the legs we found there was an endarteritis obliterans with hypertrophy of the vessels. Now we are going into this very carefully at autopsy. No matter what is wrong with the patient, we are looking at the skin of the legs. There is some indication that in our Jamaicans there is a certain amount of endarteritis and muscular hypertrophy in the arterioles and arteries of the subcutaneous tissues of the leg. These are very preliminary observations.

AYKROYD: I wanted to ask Dr Chavarria what proportion of the cases he sees show these acrocyanotic changes?

PEÑA CHAVARRIA: About 5% of our cases.

AUTRET: I wish to draw your attention to a work published by Dr Rodrigo Loria Cortes in 1949 entitled *Relaciones entre la Acrodynia y el Sindromo Policarencial en las Infancias*. These cases were observed in the Hospital San Juan de Dios, San José, Costa Rica.

SANTOS: Speaking as a clinician, I would like to suggest that before we finish this discussion, we should arrive at some practical conclusions on how biochemical methods can help the practical clinician to make an early diagnosis of malnutrition and also to follow the evolution of the disease. I think Dr Waterlow's methods of measurement are too difficult to be employed in clinical tests. Dr Dean has spoken about some others which I think are more practical, and I would like to have more emphasis put on those methods. How far can we rely on them? Can we rely on them to make an early diagnosis, and to follow the progress of the disease? I would like, for instance, to ask Dr Dean if he has seen a case of kwashiorkor with a normal level of total plasma protein?

SÉNÉCAL: I also want to discuss the chemistry with Dr Dean for a moment. We have investigated sixty-four children, and the complete picture was about the same as that described by Dr Dean: almost all our children were malnourished and many of them had infectious or parasitic diseases as well. We found, as he did, that there was always hypoproteinaemia with a rise in the levels of γ-globulin and α-globulin. We also found a reduction in amylase. As for the lipid and cholesterol, our results were variable. But I want to ask Dr Dean, what is the role of dilution of the blood in causing hypoproteinaemia and a fall in amylase? I think it is difficult to appreciate this without measuring the blood volume. That is the first question.

Secondly, we tried to find in normal children what are the normal levels of the blood proteins, and we find in Africans—not children but adults—many variations. For example, if we take the ratio between albumin and globulin, we find in normal adult Africans that it is only 0·90–1·2 (normal ratio in Europeans is 1·5), and I think, therefore, it is very difficult to interpret the results obtained in kwashiorkor.

We are at the moment trying to find a biochemical test to help us make the diagnosis of mild or early kwashiorkor, because I think the diagnosis of acute kwashiorkor is very easy and gives no trouble. Perhaps serum amylase is one such test. I don't know. I put that question in the hope that in this way we may find some test at the beginning, before the trouble sets in.

CLEMENTS: Would you like to answer those questions, Dr Dean?

DEAN: Yes. Dr Santos asked me if I had ever seen a child with kwashiorkor with a normal serum protein, and I have. Other people to whom I have spoken have also seen normal total protein levels. I was very much interested in Dr Scrimshaw's statement that he sometimes sees children with abnormally high serum proteins, although not in the most severe cases. I have certainly not seen that. But remember that I have not claimed for any one of these measurements that it is a specific test for kwashiorkor. I am trying to say that, taking these tests together, perhaps we will arrive at a biochemical method of diagnosis.

SANTOS: May I interrupt you on this point? Do you think there is any change in the quality of protein?

DEAN: No. We have done fractionations of the serum proteins by means of electrophoresis; I was very much interested in that until I realized that what we were getting was very much like what has been described by Lubschez (49) in perfectly normal American children, who could not possibly be suspected of having kwashiorkor, within about 3 or 4 weeks of almost any kind of infection. Since that time I have stopped fractionation because it seemed to me that the results were not specific for kwashiorkor.

All the earlier work of Altmann (50) and others who have worked on this has shown the same thing: a large rise in the γ-globulin. There is also in the acute stage of our series of cases an abnormal fraction which I think may be of importance. It comes out in the electrophoretic patterns slightly to the left of the γ-globulin. That is, perhaps, the only point on which I would like to do some work, but it is so difficult that I haven't tackled it yet.

The albumin-globulin ratio is affected by infections, and if our children are constantly having mild infections, I think they would have albumin-globulin ratios like those we find. That is the reason why I said 'total proteins' and not 'albumin-globulin ratio' or any quality of the proteins, in advancing these diagnostic methods.

Your point about a test for mild kwashiorkor is extremely important, and I have no answer to it at all. We don't know how to diagnose the mild case of kwashiorkor, and I can only hope that we will find a way in the future.

CLEMENTS: You got a very unsatisfactory answer to your question, didn't you, Dr Santos?

SCRIMSHAW: As a further comment on blood values, we have been doing a total of some twelve different analyses on blood samples in cases of this type compared with normal children. For many of the samples the proteins have also been separated electrophoretically. It is our feeling that while the results of these determinations tell us a lot about the disease, they frequently do not tell the physician anything that he doesn't already know. Increasingly, we are relying on serial growth measurements as the best long-term indication for the physician of response to treatment.

AUTRET: There has been some work recently carried out in Tunisia on the fractionation of globulins (51). This work shows, as already known, that in the forms with oedema, globulins α_1 and α_2 and to a lesser extent γ are increased; but it also shows, and this is new, at least to me, that in the forms without oedema, it is the globulins β and γ which are increased.

DEAN: What is the method used? Was it a chemical method or free electrophoresis or paper electrophoresis?

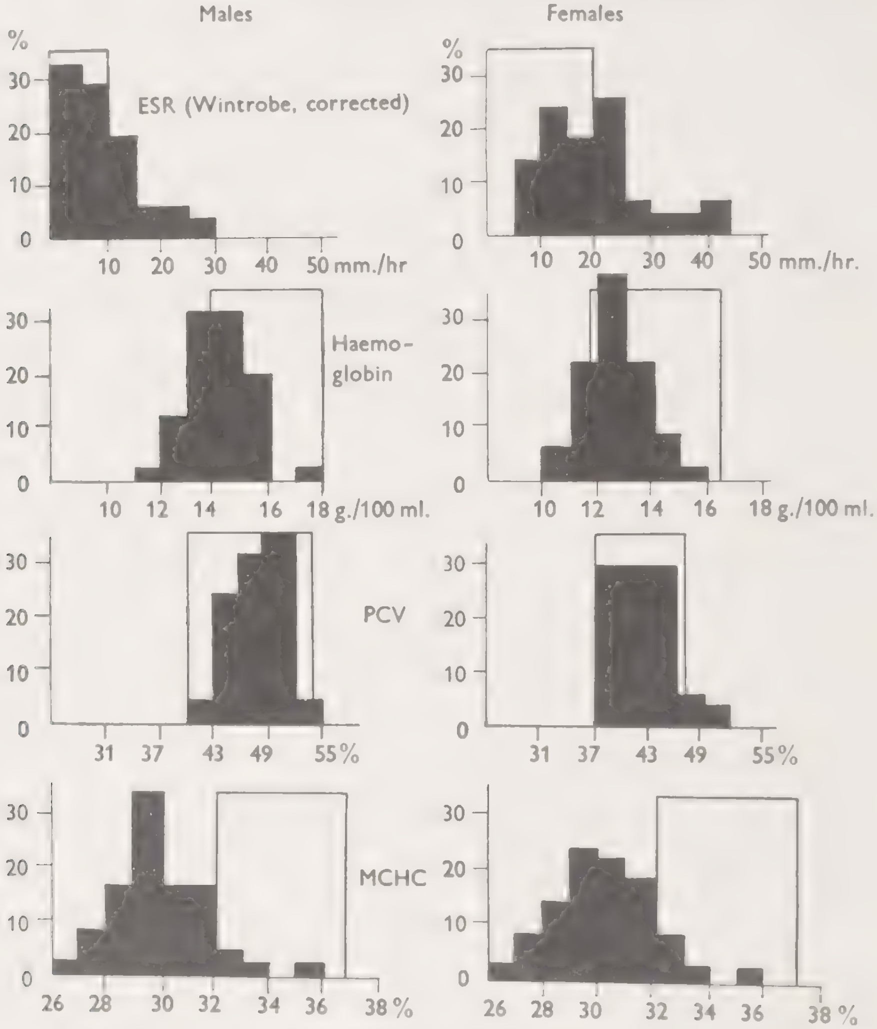
AUTRET: Free electrophoresis.

HILL: It seems to me that when we are considering the simple biochemical tests, such as albumin-globulin ratio, we ought to know what is usual in our area. Dr Rao made this point, and Dr Scrimshaw has mentioned how the pattern is almost the same in the normal and in cases of malnutrition except when they drop down steeply. For this reason we have made some measurements in my department on a hundred apparently healthy Jamaicans. I think the findings are somewhat salutary. In our series the haemoglobin levels mostly fell in the lower half of the normal range, whereas the packed cell volumes tended to fall in the upper half (Text-fig. 7). When I say 'normal' I mean what is considered normal in England and the U.S.A. (52).

SCRIMSHAW: May I interrupt to say that the same phenomenon is observed in Central America. There is a tendency to macrocytosis, even without anaemia. Supplementary feeding programmes at times result in a reduction in the percentage of macrocytosis with no significant change in the incidence of anaemia.

HILL: Unfortunately, I have no figures for mean cell diameters. I am going to suggest that this phenomenon is due to a diminished plasma volume. The mean corpuscular haemoglobin concentration (M.C.H.C.) showed the greatest deviation from normal, being usually about 29%. This, I think, would generally be taken to represent quite a severe degree of hypochromic anaemia. This is the only measurement which is not in any way affected by changes in plasma volume. The total serum proteins, determined by the biuret method, tended to fall on the high side of the normal range (Text-fig. 8). This, again, would support the suggestion that there has been a diminution in plasma volume.

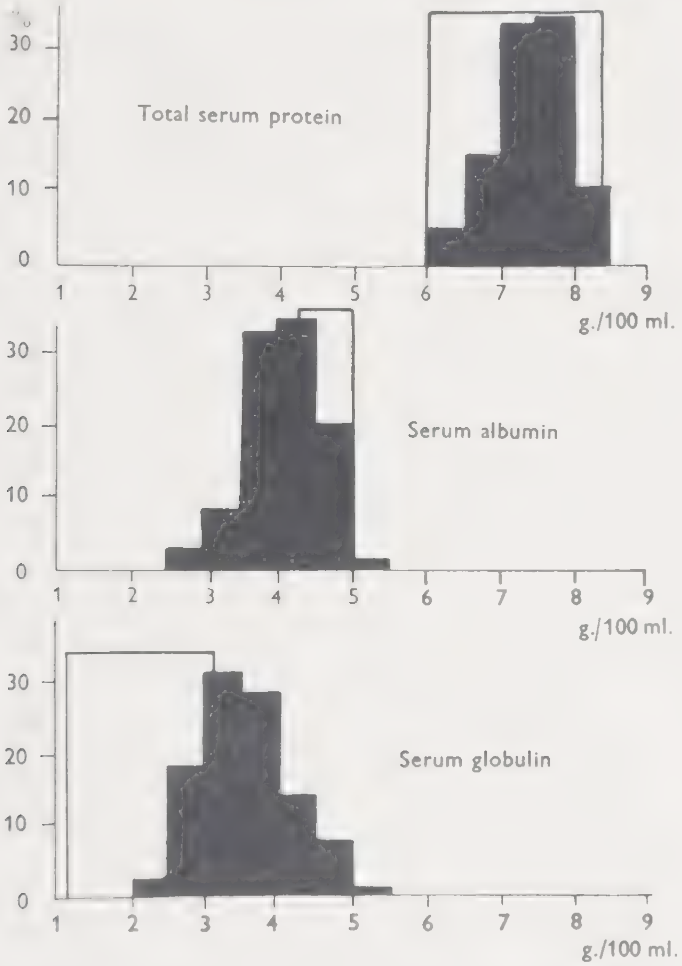
Finally, we have measured the albumin:globulin ratio, the fractionation being done by precipitation with sulphate-sulphite mixture. The mean ratio for this series was 1·2. The results have been checked by paper electrophoresis, which gave a mean value for the A:G ratio of 0·89. The normal value by the salting-out method might be taken as about 1·5. Our mean figure of 1·2 therefore represents a reduction, but not a reversal.



Text-fig. 7. Average haematological values in healthy Jamaicans. The white areas show the accepted normal range.

As I have mentioned, it seemed paradoxical to find evidence of a severe hypochromic anaemia, as shown by an average M.C.H.C. of 29%, in the presence of a high packed cell volume. A possible explanation is that a reduction in serum albumin causes a fall in plasma osmotic pressure and hence a fall in plasma volume. Thus the increase in packed cell volume, total serum protein, and in some cases of serum globulin, would be apparent rather than real.

CLEMENTS: I will now ask Dr Waterlow to give us a brief, uninterrupted summary of our discussion on the biochemistry of this problem in terms of 'where do we go from here?' It is not a summary of known facts unless they relate to that question.



Text-fig. 8. Average serum protein values in healthy Jamaicans. The white areas show the accepted normal range.

WATERLOW: I will do my best. I can summarize the discussion in general terms only. I think it emerges that there are two main ways of approaching this problem of protein malnutrition, and these two ways of approach correspond to the distinction that I made at the beginning between two planes of thought—one concerned with processes, and the other concerned with description. Dr Fremont-Smith's psychiatric technique, painful though it was to me, was successful, in that I realized much more clearly at the end of the day how these two approaches are complementary and should lead to the same point, whereas at the beginning I tended to feel that they were antagonistic. I tried to focus attention not on the clinical or biochemical picture, but on the underlying process, and I put forward the following arguments:

First, clinical experience has led us to believe that 'protein malnutrition' is an essential feature of kwashiorkor and allied states.

Secondly, 'protein malnutrition' is a vague term and may include a number of different states or processes, but, brushing subtleties aside, I went on to suggest that the cardinal feature is a depletion or reduction of the amount of protein in the organism.

Thirdly, if this idea is accepted, without destroying the simplicity of the central and obvious concept of a protein-depleted organism, we must bear in mind that the pattern of depletion may not be always the same in the different organs or tissues. It may depend on factors such as the nature of the protein depletion, the calorie intake, the chronicity, etc.

Fourthly, I suggested that we should concentrate on finding means to measure the degree of protein depletion of the body—a point I will return to shortly.

In general, I formed the impression that these ideas were accepted by the meeting, although regarded as somewhat theoretical. Discussion centred on two things: the effect of calorie intake on protein depletion, and methods of assessing the degree of depletion.

On the question of calorie intake, it was agreed, I think, that higher levels of intake, such as are postulated in kwashiorkor as opposed to marasmus, should reduce the rate of protein depletion, since undoubtedly they diminish the nitrogen loss. It may be, as Professor Gyorgy has said, that the nitrogen retention that occurs with a higher calorie intake affects some organs more than others, that the nitrogen is retained, perhaps, in muscle but not in the liver and pancreas; in other words, the pattern of depletion may be different under different conditions. But we have no information about this. Our discussion on the effect of calorie intake led on to the question of the influence of calories or carbohydrate in promoting a fatty liver, and the significance of the fatty liver. Is this fatty liver an index of the severity of the protein depletion or is it an irrelevant effect superimposed, as it were, on the depletion?

It is no part of this summary to try to answer those questions, but this part of the discussion suggested the following lines of inquiry:

First, animal experiments, to see how variations in calorie intake and indeed, in other factors, do modify the effects of protein depletion, and what alterations of pattern they impose. Of course, a good deal of work has been done on these lines, but judging by the few specific experiments that were quoted in the course of the meeting, it seems to me that a great deal still remains to be done.

The second main line of inquiry in relation to this particular point, the calorie intake, was the need for widespread and accurate evaluation of the diet that leads to kwashiorkor and fatty liver. Is it or is it not relatively high in calories or carbohydrate? This, of course, has been done to some extent by Drs Autret, Gopalan, Rhodes and others, but the data are insufficient and inconclusive. More accurate and more extensive data should be collected, although the practical difficulties are admittedly great.

The other main topic of discussion under this first heading, 'Processes', was how to measure the degree of protein depletion. Of the methods suggested the first was the classical technique of nitrogen balance. Dr Dean felt that this was not of much value in the type of case that he deals with. I think that this point needs further discussion, as it seems to me that the measurements ought to be valuable, and I hope to raise this topic again later.

The second line of approach is by measurements of body composition, such as were illustrated in Dr Gopalan's most valuable work. A good deal of thought must, however, be given to the technical aspects of these measurements if results are to be reliable and, above all, if they are to be comparable when carried out in different places.

Thirdly, I spoke about measurements of the composition of individual organs, such as the liver. But these, as I tried to emphasize, can never give a clear-cut answer to the problem of how depleted is the body as a whole, because the liver is only one organ and a very specialized one. Such measurements merely give a clue to what is happening; they should, perhaps, be extended to other organs, particularly to muscle, which, after all, is the biggest reservoir of protein in the body.

Fourthly, a possible line of inquiry would be by measurements of protein turnover by isotopic methods; possibly, although I know very little about these techniques, one would be able, by a kind of isotope dilution method, to obtain some measure of the amount of active protein in the body, as well as its rate of turnover.

I sensed that the meeting regarded all this as rather theoretical, and it was pointed out with justice that these methods of inquiry which I have mentioned are difficult and not suited for routine work. That is quite true, but I wish for a moment to see just what is involved.

If we adopt the reasoning that I have set out, we jump, as it were, right into the middle of the problem, and from that middle we follow various paths that open up from the central concept of protein depletion. Of course, this central hypothesis or concept may be wrong; but if it is not wrong, if we could succeed in measuring the degree of protein depletion and in observing the variations in pattern that may occur under different conditions, then we could fit these results to the clinical picture or the various clinical pictures. Then we would have a really sound basis for clinical and aetiological differentiation, and we should have a base-line for assessing the value of measurements that we think might be useful as diagnostic criteria. For instance, if Dr Gopalan had a hundred measurements of body composition, I could ask him how the plasma cholinesterase correlates with them. At the moment, we have no idea, really, what a measurement like that of plasma cholinesterase means. Therefore there is some practical as well as theoretical use for these difficult fundamental studies, and the fact that they are difficult makes it all the more necessary to discuss them at a meeting such as this one. One of the difficulties is a geographical one; where the clinical material is most rich, it is often hardest to assemble the men and resources for investigation. This, perhaps, is an indication for international cooperation.

Now I come to the second line of approach, the descriptive. In the first place, this involves detecting and collecting deviations from the normal, whether clinical or biochemical. Under this heading there were described at various points in this meeting changes in blood proteins, in blood enzymes, in excretion of antidiuretic substances, etc. One aspect which was not mentioned and which ought to be, and which I hope will come up again later, is changes in carbohydrate metabolism. The question immediately arose and kept recurring in the discussion: are any of these things which various people have found and studied diagnostic criteria? Are they specific? Can they be used as tests for kwashiorkor? Put in that form, I think such questions are sterile. If we use words in a strict way, there can be no such thing as a biochemical test for a clinical syndrome.

In scurvy, for instance, we expect to find a low ascorbic acid level in the blood, but this may be found without the disease, as a clinical disease, being present. A clinical syndrome, in my view, can be diagnosed only by clinical means. A biochemical test can demonstrate only the presence or absence of the biochemical process—as, in the above example, a deficiency in the body of ascorbic acid. When we know the pathogenesis of a syndrome, the two things come together. In diagnosing kwashiorkor, one relies, in my experience, on laboratory aids and confirmation much less than one does in many other diseases. I think, therefore, that the search for a test for kwashiorkor which will distinguish it, say, from marasmus, must be sterile and is a waste of time when looked at in that light, until the questions put in the first part of this summary have been answered.

But we can look at the matter in another and more profitable way. The search for a specific biochemical change in kwashiorkor or anything else really means the study of associations. We have a phenomenon like, say, a low plasma cholinesterase or an altered partition of cholesterol and its esters, such as Dr Dean described, and we want to know what other phenomena, clinical or biochemical, these changes are associated with. Clearly, if one puts the question in this way, it is necessary to test the associations over the widest possible range of conditions and different types of case, and it must be admitted that where this has been done, most of the types of measurement that were mentioned yesterday do *not* seem to be linked with any closeness to any particular clinical picture. The things which were mentioned, time and again, seemed hopeful but then proved rather disappointing. However, I don't think that this matters. To me, the importance of the associations that may be established between a given biochemical change and other biochemical or clinical features, is not the help they may give in diagnosis. I don't think the problem of diagnosis should worry us. Rather, the associations that may be found should give a clue to the meaning of the phenomena observed, since science advances by the analysis of associations.

To give another example, I think that I have observed an association between red hair in infants and liver damage. It may or may not be true, but assuming that it is true, I don't need this fact for the purpose of diagnosis. But if I follow it up to find *why* the association occurs, it would tell me a great deal about the cause and nature of both types of change.

And so, to end, the importance of studying all the biochemical and other changes that may be found in kwashiorkor, marasmus and other states of malnutrition, is, I think, that each alone means relatively little, but each, if followed up, may give a clue to the nature of the underlying process. Is enzyme production low, because of damage to specific organs, or because of shortage of building blocks? These questions follow from the finding of low levels of various enzymes in the plasma. Again, as Dr Gopalan showed us, the antidiuretic substance seems to be in excess because, perhaps, of functional liver damage. First he found the phenomenon, and then he analysed it. At each point one can go on taking a further step, as he has done.

Clearly, if we have to sketch work for the future, as many questions of this kind should be asked and answered as possible. I don't think it is possible here to specify in any detail the types of work to be done or the approach to be adopted, but if all these various lines are followed up, it means, it seems to me, that we are coming in from various directions, and by various paths, from the periphery to the centre of the problem. In other words, the two lines of approach that I mentioned at the beginning meet. One starts at the middle and tends to radiate outwards; the other works from without inwards.

It may seem that I have, unfairly, put my own views rather than summarized the discussion; but I have tried to recapture what seemed to me the rather inconclusive outcome of the final part of the discussion—the significance and object of all the various measurements that we make—and, as far as I can, to draw it towards some conclusion.

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SECOND SESSION

PATHOLOGY OF PROTEIN MALNUTRITION

Bras: Having been invited to talk this morning, I had to ask myself whether it is still justified for a pathologist to say something at a meeting on protein malnutrition. People like Dr Waterlow have taken up biochemistry because they felt that it might give them an approach to the problem where the microscope failed. When we look back at the excellent work of Dr Davies in Uganda, Dr Carvalho in Brazil, and Dr Veghelyi in Hungary, we come to the conclusion that histologists served the purpose of drawing attention to particular organs, after which the biochemists took over, more or less.

Dr Waterlow makes me feel good when he says that he needs me to tell him whether or not the liver has an extra amount of infiltrative cells, because that would change the evaluation of his biochemical findings. Professor Cameron, again, has recently published a big volume called *The Pathology of the Cell* (1), obviously putting prominence on cytology rather than histology. But there is a ray of light here. In a survey of the literature, he comes to the conclusion that, after a period in which pathology was largely defined in terms of biochemistry, morphology now once again seems to come into prominence, though not morphology as observed by the ordinary histologist, like myself, through an ordinary microscope, but rather submicroscopic structures, investigated by special techniques. We already have interesting observations on submicroscopical changes in disease. The biggest drawback in this type of work is that no mean knowledge of physics and other basic sciences is needed, and it will largely become the work of teams of specialists to carry out an approach like this.

Therefore, I appear before you convinced that only a feeling of extreme modesty befits a member of the genus histologist, working with the ordinary microscope.

When we review how far the histologist has been of use, we have to refer back for a minute to the fact that studies of the malnourished and undernourished individual largely fall into two groups; the first group is one where people who have previously been well fed are subjected to a period of acute starvation or malnutrition. This group, as we all know, is found in concentration camps, famines, wars, and also experiments such as have been carried out by Keys (2) in Minnesota. The histologist has usually had little opportunity to come in here.

I am looking forward to what appears to be the one great exception to this field, that is, the work of the Jewish doctors who were locked up in the Ghetto in Warsaw (2) facing extermination, and who wrote down their experiences for posterity, knowing that they themselves would never see their work in print. According to an extract which I read, this work includes the findings in about 3600 autopsies.

The second group is concerned with the malnutrition that exists in the underdeveloped areas of the world. Here the histologists came in when the so-called civilized part of the world began to take interest, after the pioneer work of Dr Williams and others.

Before going any further, I should like to make an observation which has also been mentioned by Dr Davies in one of his reviews, that there is reason for some concern about the co-operation between workers in the tropical and in the temperate zones. It struck me, when I was reading the Danish report on observations made in concentration camps (3)—a report which has no less than some 480 references—that no reference was made to the work of Dr Williams, Dr Trowell, Dr Autret, or even to the book of the Gillmans (5), although there is mention of work done in India by Drs Aykroyd and Gopalan, and of Dr Rao's experiments. I don't think it can be dismissed entirely by saying that people like us are to a great extent studying infants and children, whereas those other people have been studying adults. Also, the chronically undernourished individual in tropical countries, surrounded by parasitic infections and other stresses, is admittedly not entirely comparable to his acutely starved counterpart in the temperate zone. I feel, however, that if co-operation is not there, workers in both temperate and tropical zones must lose. Here again I am very grateful for having been allowed to partake in this conference, because I feel that it offers possibilities in this respect that are usually not easily achieved.

If I may come down to the actual topic of this morning, I have, as the starting-point, selected for discussion the liver, on the strength of Dr Fremont-Smith's suggestion that the introducers should devote a large part of their time to the work in which they themselves have been engaged most extensively.

As to background, I cannot yet give you much information about the average Jamaican liver. We have been looking at livers of children with non-hepatic as well as with hepatic diseases, including livers from children who were not ill at all; we have some 150 livers in this group. We have also started to collect material from people who died an accidental death, following what the Gillmans (5) have done in South Africa, and we have about thirty such livers. If we continue long enough, it is clear that in time we will have an idea of what the average liver is like of the average man who is accidentally killed. I cannot tell you too much about this, because we do not have sufficient material, except that the average liver so far has been quite normal in aspect. Certainly, there are not the changes present in practically every African liver, according to the reports from Uganda and South Africa.

There is one condition to which Professor Hill has been calling attention for a long time; that is, a thickening of the wall of the hepatic veins, or of the branches of the hepatic veins, a condition which has been variously termed collagenosis or perivascular cuffing, both terms speaking for themselves. We have repeatedly discussed this between ourselves, and we do not know the significance of it.

FREMONT-SMITH: Do you mean that you find this in the average liver or only in the sick ones?

BRAS: No, we find it in many livers, in the non-hepatic as well as the hepatic cases.

RAO: In children or in adults?

BRAS: In both children and adults.

CRUICKSHANK: Is the process virtually the same in the child, histologically, as the adult?

BRAS: Yes. The name 'collagenosis' is a very good one. It indicates that there is a thickened vein wall, which gives the tinctorial reactions of collagen; it is the same in children and in adults.

CLEMENTS: What is the youngest age at which you have observed it?

BRAS: I have not gone into this question particularly, but I think that I have demonstrated it even in the newborn.

WATERLOW: Does it include thickening of the reticulum fibres around the veins?

BRAS: It does not, to any convincing degree. One might occasionally find in that area a questionable thickening of the reticulum fibres, but that certainly is not a constant finding. I don't know what Professor Hill thinks about this.

HILL: I would say that there is often thickening of the reticulum fibres. The thickened vein walls stain like collagen, and at a later stage you certainly see fibroblasts. The histologists may differ, I think, as to how this thickened wall came about, whether it was a reactive fibrosis or a deposition of something.

BRAS: Do I understand you to say, Dr Hill, that the fibroblastic reaction is there in all these cases, in the later stages?

HILL: You can see, in the later stages, long spindle cells.

BRAS: In the adult, in other words?

HILL: Yes, in adults. Sometimes, later, the vein wall becomes hyaline and looks just like what we call scar tissue.

GYORGY: Is the thickening extralobular or intralobular?

BRAS: It is in the hepatic venous tree, in the centre of the lobule.

GYORGY: Do you have cellular infiltration too, around the vessel? Not fibroblasts, but small cells?

BRAS: No, there is no cellular infiltration and, in my opinion, no thickening of reticulum to any important extent in these cases.

GYORGY: And around the larger branches of the hepatic vein?

BRAS: No, there is no difference between the larger and the smaller veins in this respect.

HILL: I think I would agree with that. I haven't seen any cellular infiltration, meaning small round cells, which might suggest that there had been an active process in the vein wall or, perhaps, degeneration of the parenchymal cells around the veins.

GYORGY: That applies for the time being to the so-called average liver?

HILL: Yes, the average Jamaican liver. This has been an interesting finding to us. When I was in Indonesia, which was Dr Bras's stamping ground, I was shown some livers there, and I saw nothing like that. Just recently, I was in Newcastle and I saw some livers in Sir James Spence's department. I was worried for fear we were seeing something that was average or normal in European livers, but this seems not to be so. I have, for instance, a European child 7 months of age, and I can show you a Jamaican child aged 1 year, and you will see that there is quite a difference in the perivascular cuffing. But that is for later.

BRAS: I think this lesion has no differential diagnostic value, because it occurs in all sorts of conditions.

RAO: What is the stain for these histological preparations?

BRAS: The ordinary stain is haematoxylin-azophloxin. If we want to stain connective tissue we usually use Mallory's trichrome stain; another very popular stain in my own hands is a combination of orcein and fast green F.C.F.

RAO: Any particular stain for reticulum?

BRAS: When we stain for reticulum, we use the modified technique evolved by Lendrum (6).

Having dealt with the background, let us proceed to the hepatic conditions we have seen which we think important, and of which I want to give you a sort of cross-country view.

I should like to start with the condition that leads to infantile cirrhosis, a disease which is rare in other parts of the world, except India, as far as we can see.

Before I start, may I define the term 'cirrhosis'. The condition is meant to be one exceeding a certain degree of periportal reticulin increase or monolobular fibrosis; i.e. that condition whereby there is a true distortion of the liver architecture because of fibrosis, followed by development of collateral circulation, hepatovenous shunts, etc. The condition is rare in children (7, 8, 9), except in a few places in the world where it occurs more frequently: (1) India (10), (2) Jamaica (11, 14), (3) Sangir (12), (4) West Africa (13). Detailed histological studies of this condition have been reported by Rao (10), by Hill *et. al* (11), by Blankhart (12), by Walters & Waterlow (13) and by myself (14). It is notably absent in areas comparable to those mentioned, viz. Indonesia, Curaçao, and other regions in Africa. Again, in Brazil, although there is much kwashiorkor, no infantile cirrhosis has been reported; Dr Van der Sar (15) in Curaçao made similar observations and so did Dr Meneghello (16) in Chile. Rao has described histologically the picture seen in infantile cirrhosis in India and his conclusion is that this is a form of toxic cirrhosis. He describes changes in the hepatic vein which he considers very important in the evolution of the cirrhosis. I think Professor Hill might like to describe his own findings later. Blankhart (12), working in Indonesia, found a periportal fibrosis and cirrhosis running more or less *pari passu* with, or seemingly following upon, a stage of fatty change. He thinks that, owing to the few observations that he could make histologically, he is not justified in doing more than point at the similarity to the picture in regions of Africa and elsewhere in the world where fibrosis seems to follow fatty change. Walters & Waterlow (13) saw a fibrosis starting in the portal areas and infiltrating into the surrounding parenchyma; this occurred in infants and children who did not show the preceding severe fatty change typical of kwashiorkor. Aetiologically they suggested a combined action of (*a*) malnutrition, and (*b*) malaria. I myself have been observing a condition in children here which is in many respects like Rao's in India. I believe that the main change is an occlusion of the hepatic veins. Therefore I have called it venous occlusive disease (V.O.D.).

The clinical picture in our cases is not distinguishable from the cases of McFarlane & Branday (17) and of Royes (18), of which unfortunately practically no histology is known. It is also very similar to the picture described by Hill & Rhodes as serous hepatosis (11).

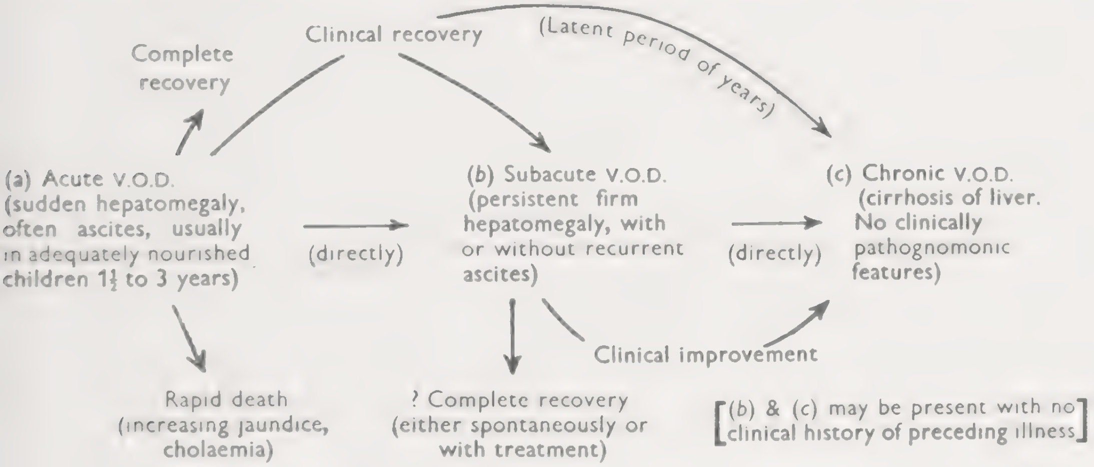
Dr Stuart will perhaps outline the clinical features of our cases of V.O.D.

STUART: The first picture Pl. 2 (1) is of a case of acute V.O.D. This is a fairly typical example of the earliest presentation. The onset is usually in the age group 2–5 years. It is frequently preceded by an acute infection, usually of the upper respiratory tract. This case has oedema and enlargement of the liver, and there are other minor signs of malnutrition. These children are frequently under weight and under height for their age, but they seldom have gross signs that are seen in the classical case of kwashiorkor. This acute phase is very unpredictable in its response to treatment. The patients often settle in the course of a few days and usually in a few weeks. They may lose their oedema and become clinically normal. The hepatomegaly frequently disappears completely. On the other hand, further progress toward the second stage sometimes occurs.

Hill: Is the oedema generalized?

Stuart: It is usually confined to the legs. Only very occasionally is it generalized.

Pl. 2 (2) shows the subacute stage of the disease. In this stage a considerable hepatomegaly usually persists. There are often frequent recurrences of at least minimal, and sometimes considerable, ascites. Response to treatment at this stage is again variable, and usually slower than in stage one.


Complete recovery
Clinical recovery
(Latent period of years)
(a) Acute V.O.D. (sudden hepatomegaly, often ascites, usually in adequately nourished children 1½ to 3 years)
(directly)
(b) Subacute V.O.D. (persistent firm hepatomegaly, with or without recurrent ascites)
(directly)
(c) Chronic V.O.D. (cirrhosis of liver. No clinically pathognomonic features)
Clinical improvement
Rapid death (increasing jaundice, cholaemia)
? Complete recovery (either spontaneously or with treatment)
[(b) & (c) may be present with no clinical history of preceding illness]

Text-fig. 9. Clinical natural history of veno-occlusive disease of the liver (as suggested by present evidence).

Although classed as subacute, the child shown in Pl. 2 (3) is probably in a later stage between the subacute and the chronic. In addition to the hepatomegaly there is a congestive splenomegaly, indicating that there is now a considerable portal obstruction.

In the third or chronic stage Pl. 2 (4), you will see that the child is obviously malnourished. The liver is again enlarged, but it is now much firmer in consistency. The spleen also is enlarged and almost stony hard. At the point marked by the circle in this child there was a venous hum audible in both systole and diastole, which we associated with aneurysmal dilatation in the veins of the ligamentum teres which we found at post-mortem.

McCulloch: Of what did the child die?

Stuart: He died of haematemesis. I should have mentioned also that sometimes we see two or three children in a family develop acute V.O.D. simultaneously.

Text-fig. 9 shows our conception of the clinical natural history of v.o.d. as suggested by the evidence that we have at present available. It summarizes what I have said before. There is frequently complete clinical recovery from the acute episode with no recurrent episodes and with return of a normal liver picture, as judged by biopsy specimens. On the other hand, cases sometimes present again in the subacute phase of the condition after apparent clinical recovery, or they may pass directly without any improvement from the acute to the subacute phase.

Occasionally death occurs in the acute phase of the disease. We have seen only one case of this type; this closely resembled the clinical description given by Dr Rao (10, 19) in his account of Indian infantile cirrhosis. There were continuous ascites, rapid development of jaundice and hepatic failure, and death in hepatic coma.

Complete recovery again may occur in the subacute stage; but often the children pass through a phase of apparent clinical recovery into the chronic stage of the disease.

We regard the chronic stage as progressive, self-aggravating and irreversible. There may again be some apparent clinical improvement, but the liver biopsy specimens remain unchanged and sometimes show progressive fibrosis. Clinical follow-up usually shows gradual deterioration. We have seen six children in the chronic stage of the disease, three of whom presented with haematemesis; and I put it to you that these children develop signs of portal obstruction and oesophageal varices earlier than do cases of Laennec's cirrhosis. I don't know whether Dr Bras would agree, but a liver lesion that is primarily vascular will presumably produce portal obstruction earlier than one in which the vascular changes are secondary, as in the case of Laennec's cirrhosis.

It would also appear that most of these patients die quite early after this third stage is established. We see relatively few cases of any form of adult cirrhosis and certainly very few of chronic v.o.d. We have had only one case of chronic v.o.d. in an adult, and that was in a girl of 19 years.

Cruickshank: I don't agree with Dr Stuart's last remark. I think that we have a relatively high incidence of cirrhosis of the liver in young adults and in later age groups.

Stuart: Although the over-all incidence is high, I think that adult cirrhosis is still not as frequent as one would expect from the high incidence of liver disease in children. There is certainly a low incidence of adult v.o.d.

One further point: the clinical behaviour of these patients is so variable that it is difficult to assess the effects of any particular method of treatment. It is also important to relate any apparent response or lack of response to treatment, to the stage of the disease at which it was begun. Otherwise the results might be misleading. The early stage frequently responds readily, while, as is to be expected, the chronic stage is usually very intractable.

McCulloch: You don't correlate the stage of the disease with the age? What is the time factor?

Stuart: The time interval between one stage and another is very uncertain. It may be weeks, months or even years. Our chronic cases fall, for instance, between 4 and 19 years of age.

Rao: Is there any jaundice at this stage?

Bras: Yes; however, it is variable, and we have the impression that it is less frequently seen than in your cases; also our cases on the average seem to be a little older than yours. Would Dr Stuart agree to this?

Stuart: Yes. We have seen only one case in which we think the clinical picture agrees entirely with Dr Rao's findings, a child aged 10 months, with oedema and jaundice, who rapidly went into hepatic failure and died. Our other acute cases usually recover.

Rhodes: There is another possibility which Dr Stuart did not mention in his outline of the natural history: not only may acute v.o.d. lead into the subacute stage, but subacute v.o.d. may develop into the acute disease. We don't really know which is the initial stage of this disease. Whilst acute v.o.d. is relatively rare, subacute v.o.d. is, I think, very common indeed. In a random sample of over 500 poor-class children, 47 % had liver enlargement. It is possible that a child with an abnormal, enlarged liver may, under additional stress, blow up into an acute case of v.o.d.

You may ask if the 47 % of children with hepatomegaly were cases of v.o.d. I am not certain whether all of them were, but I know that some were, and the clinical picture and background were similar in all of these children. Thirteen had liver biopsies and, of these, eleven showed lesions which Dr Bras will describe—venous occlusion or diffuse fibrosis or both. Therefore, a small number of cases from this large group of children with hepatomegaly showed, histologically, the liver lesions of v.o.d.

Waterlow: I think it is worth emphasizing that sometimes you get a mixed picture of kwashiorkor and v.o.d. This happens particularly in the youngest age group. We have had cases, aged about 1 year, in which the liver was both fatty and showed the histological changes of v.o.d.

Williams: I think when Dr Bras says that juvenile cirrhosis is rare in different parts of the world, it may exist, but is not reported. We used to see cases of cirrhosis on the Gold Coast in my day, but there simply wasn't time to report everything.

Peña Chavarria: I would also like to say, Dr Williams, that we see cases of jaundice in young children in Costa Rica.

Gyorgy: How old?

Peña Chavarria: Up to 3 or 4 years.

Gyorgy: With ascites?

Peña Chavarria: Yes.

Bras: I can add to Dr Williams's observation. Our paediatrician, Dr Jelliffe, who is away on a W.H.O. assignment, wrote me from Egypt, saying 'I see veno-occlusive disease here'. We hoped to have some histological slides from Egypt for this meeting, but I have not yet received them. I am glad that Dr Williams is so positive about this. There is thus some evidence that the condition occurs in other places, but that it has not been reported.*

Waterlow: I think Jelliffe said he had never seen anything like it in Nigeria or the Sudan. We never saw it in the Gambia, although we were looking for that kind of thing, and no doubt so was Jelliffe.

Bras: Yes, I agree. The fact is, however, that as we now know from Dr Peña and Dr Williams, and from Dr Jelliffe's visit to Egypt, there must be places where it has been overlooked or in which it has not been reported.

Williams: The reports are only clinical, not pathological.

Bras: Let me now show you the histology of this condition. This is a picture with which I would like to start because we believe that it is one of the earliest manifestations of this disease (Pl. 3). It is evident that there is congestion localized in the centrolobular area, and that the congestion and widening of the sinusoids is frequently so great that the liver cell cords disappear.

Gyorgy: In the central area?

Bras: Yes. This is the centre of the lobule. Sometimes neighbouring sinusoids coalesce into what we like to call blood lagoons. The liver cell cords are compressed, and groups of liver cells become dissociated and isolated inside the blood lagoons.

Fremont-Smith: When you say that they are dissociated and isolated, did you follow them through in serial sections? Are they really islands or are they, perhaps, cords which run longitudinally?

Bras: Theoretically speaking, there could be a row of liver cells perpendicular to the plane of section. The fact still remains that they have become detached from their neighbours in the plane of section. This figure, Pl. 4 (1), is an affected vessel in an early stage. What I want to bring out here is that the lumen is occluded by cells, varying from cells of a large phagocytic type to lymphocytes, plasma cells and an occasional polymorphonuclear leucocyte. This occlusion is due mainly to a swelling of the intima; the media and the adventitia are relatively very little involved. It is possible that this thickening is caused by seepage of material under the intima. What this material is, in the early stages, is not known. It is optically translucent, and looks like oedematous fluid. In this stage, Pl. 5, you see a cobwebby structure of connective tissue, and there is an occasional cell of the type which I have already mentioned. Sometimes blood may be seen underneath the intima. The easiest explanation of this is that the intimal lining is so thin that it is readily ruptured, and blood seeps underneath. There is sometimes so much blood under this intima that it looks almost like a dissecting aneurism.

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* A reprint of an article on the condition in Egypt has since been received (20).—G. Bras.

Fremont-Smith: Do these red cells underneath the intima look fresh?

Bras: They look perfectly normal.

Fremont-Smith: Just like the cells inside the lumen?

Bras: Yes. I can add to this, that I have never seen any iron deposit from breaking down of erythrocytes there. In all these blocks differential stains for iron were done.

Hill: Is that a biopsy or post-mortem specimen?

Bras: This is a post-mortem liver.

Hill: Good. So that, in fact, the haemorrhage cannot be an artefact? It was there when the patient died?

Bras: That is right. The media also tends to be slightly thickened, and there is a widening of the lymph vessels of the adventitia. Finally, I might recall a point made by Dr Waterlow, that this lesion and a fatty change in the liver are not mutually exclusive.

This figure, Pl. 6 (1), is the condition, as shown with a reticulum stain, when it has been going on for some time. What you see is a centrolobular fibrosis. The figure shows the centrolobular vessel. It is surrounded by an increased amount of reticulin fibres as well as by thickened pre-existing fibres. The portal area is unaffected.

Gyorgy: Is this fibrosis or just condensation of the reticulum?

Bras: There is a thickening of the reticulin fibres, but I also definitely think that there is an increase in the circular Gitterfarsern of the sinusoids.

Rao: A thickening as well as a condensation?

Bras: I think it is both. Pl. 4 (2) shows a liver from the case to which Dr Stuart referred a little while ago. The child was 10 months old, and the picture is very much like the one described by the Indian workers. There is a certain amount of greenish bile staining. The child was jaundiced. A striking thing here is the mottled appearance of the cut surface. This is caused by areas of regeneration. On close inspection one can demonstrate a gelatinous intimal thickening, which partly or completely occluded the lumen of the veins.

I believe that, in addition to the change in the intima, there is sometimes also a spasm of the vein wall, because, as in this figure, Pl. 6 (2), it is often very thick, even bearing in mind the collagenosis that we know to occur frequently in Jamaican livers.

Vergara: Excuse me, but what are your reasons for believing it is spasm?

Bras: Simply the fact that spasm has been observed in experimental animals to occur in the hepatic venous tree. I may come back to this later when we discuss the differential diagnosis, if you wish.

This figure, Pl. 7 (1), is something which intrigued me very much. I tried to follow it up but I could not satisfy myself completely. This looks like a spastic vessel with a narrow lumen, and it looks as if the tributary, in trying to come in, has been prevented from bringing its blood into the vessel, and has become widened. That is the simplest explanation. I present it to you as an observation fitting in with the idea that there may be some spasm of the vessels on top of this intimal thickening. Thrombosis is a relatively infrequent thing to see, and I have no doubt that when it occurs it is secondary to the changes in the intima. Pl. 7 (2) shows, I think, the development of collateral vessels. A vessel is blocked and a new lumen has been formed next to it. As soon as collaterals develop the liver is potentially in great danger, because the circulation is short-circuited and parts of the liver may very easily be damaged by lack of vital blood supply. That, of course, sets in motion the process of further distortion. It is evident that the wide lumen shown has actually been developed through the coalescence of sinusoids. This of course is a well-known phenomenon. Pl. 4 (1) shows a vessel in which the original deposit has been completely organized, so that collagen is laid down; the black fibres are elastic fibres. Pl. 8 (1) shows non-portal fibrosis surrounding an occluded centrolobular vessel, with two unaffected portal tracts. There was abundant development of collateral circulation in other areas of the liver. In those areas the picture amounts to that of a true cirrhosis. Grossly, this liver in Pl. 8 (2) shows a finely granular cirrhosis, which is diffuse. There are collaterals running into the diaphragm.

Pl. 9 (1) shows a true cirrhosis. In many parts of the liver it is still demonstrably nonportal, as in this section.

Finally, Pl. 9 (2) shows how the condition sometimes develops into cirrhosis through repeated episodes. There are two elastic laminae (X) enclosing a collagenized intimal swelling (2) from a previous attack. The original media is at (1). A recent intimal swelling of the acute type, as demonstrated before, has developed on top of the previous one.

Mackay: Here you have shown changes in the vessels of the liver; have you searched for changes in the capillaries elsewhere in the body?

Bras: I have, in all the organs of the body that we usually examine; that is, the heart, lungs, liver, kidneys, spleen, thyroid, adrenals, pituitary and the skin.

Mackay: And you find nothing?

Bras: No.

Mackay: I don't really know what these histological changes you have shown us mean, but these vessels look singularly sick to me. If, for instance, they were in that state in the skin, I am quite certain that increased fragility would be very easily demonstrable.

Stuart: I haven't done capillary fragility tests, but there has been nothing to make me suspect that the capillaries might be unduly fragile. For instance, when we have taken the blood pressure, there hasn't been any development of petechiae.

Rhodes: I have done capillary fragility tests in cases of v.o.d. and I did not find increased fragility.

Fremont-Smith: You don't get petechiae in the retina or the sclera?

Stuart: No.

Bras: One of my points, Dr Mackay, is that this is a condition that is peculiarly present in the hepatic venous tree and nowhere else.

Mackay: That, to me, is very odd.

Stuart: Can you tell me whether, in your opinion, Dr Bras, these changes in the hepatic veins are primary in the vessels themselves or secondary to changes in the surrounding liver cells?

Bras: I cannot demonstrate a primary degeneration or a primary necrosis in the liver parenchymal cells. I think that the primary change is present in the blood vessels and is of the character that I have just shown. As a consequence of that there is sinusoidal congestion, mainly in the centre of the lobule. As a result of this congestion there is a loss of liver tissue, and fibrosis develops in the centre of the lobule. If this process is sufficiently long continued and severe, there will develop a non-portal cirrhosis, which to the naked eye looks like a Laennec's cirrhosis. However, if this goes further, it will be impossible to 'backtail' the process.

Dean: May I ask one extremely simple question? What is the connexion between this very interesting condition and protein malnutrition? You see, in my recent search of the literature, one of the things that struck me is that jaundice never seems to be reported in uncomplicated kwashiorkor.

Bras: The relation between protein malnutrition and this condition is, we think, simply this: clinical and biochemical observations suggest that these children are malnourished.

Dean: What has that got to do with protein malnutrition?

Bras: I don't know how you would prove that it is specifically protein malnutrition. I can quote you experiments from animals.

DEAN: I don't want that. I want data about children's diets.

RHODES: I have some data that perhaps bear on this question. Table 10 shows the weight deficit in three groups of Jamaican children. They are children with V.O.D., asymptomatic hepatomegaly and healthy children. Two-thirds of the forty-two acute cases of V.O.D. were markedly under weight for their ages. Of 119 children with asymptomatic hepatomegaly, 53 % were under weight, and of 155 healthy children without hepatomegaly only 27 % were under weight. All were below school age, and had a similar socio-economic background. The differences between the three groups in the percentage of children under weight are statistically highly significant.

Table 11 shows a typical diet of a child with asymptomatic hepatomegaly; it is very low in protein and also low in minerals such as calcium and in

Table 10. *Number of Jamaican children who are under weight*

(By 'under weight' is meant more than 10 % below the standard weight for the age, as given by Holt & McIntosh(21).)

Group	No. of children in group	Percentage of children under weight
Healthy	155	27
Acute V.O.D.	42	67
Asymptomatic hepatomegaly	119	53
Kwashiorkor	21	100

Table 11. *Average daily diet of child with venous occlusive disease, aged 2 years, weighing 20 lb.*

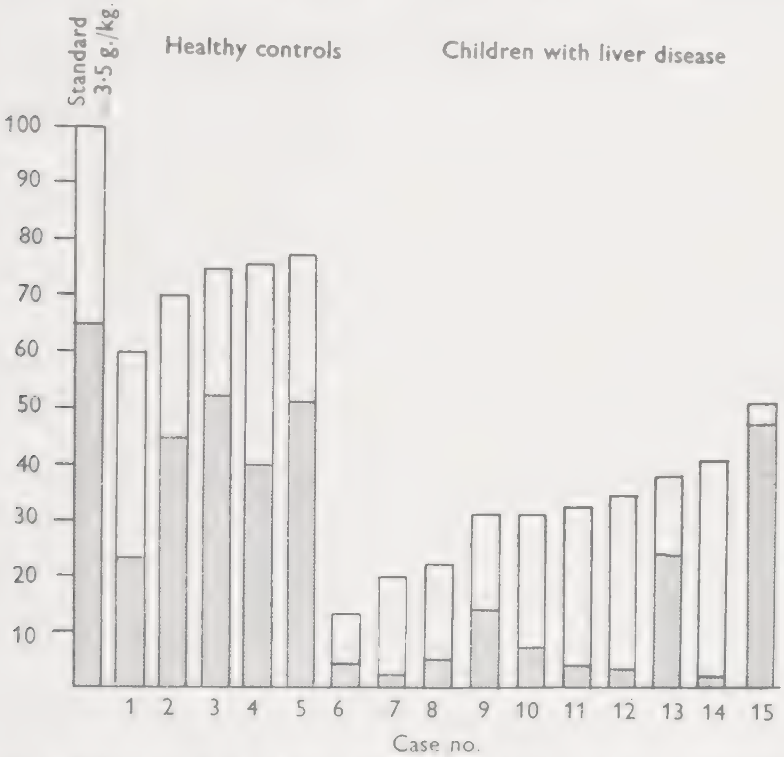
MENU

7 a.m.	Bush tea with brown sugar and condensed milk
11 a.m.	Cornmeal porridge with brown sugar and condensed milk, white bread
3 p.m.	Boiled rice with yellow yam, or plantain, or green banana porridge, or cornmeal
7 p.m.	Bush tea with brown sugar, sometimes crackers

MEASUREMENT

Type of food	Amount (g.)	Protein (g.)	Calories
Cornmeal	76·0	7·6	265
Brown sugar	119·6	0	478
Condensed milk	8·5	0·7	26·7
White bread	33·0	3·3	116
Rice	8·3	0·6	29·2
Green banana	16·6	0·2	17·1
Yellow yam	25·0	0·5	25·0
Plantain	8·0	0	8·2
Crackers	15·0	1·5	52
Total	310·0	14·4	1017·2
Requirements for age	—	42·0	1100

vitamins of the B group. Unfortunately, I have done no large-scale diet surveys, but I measured the diets of fifteen children in their homes. The results are shown in Text-fig. 10. On the left is the standard of protein intake recommended by the National Research Council—3·5 g. protein per kg. of body weight per day. The shaded areas represent animal protein and the clear areas represent protein of vegetable origin. The first five children were, to my knowledge, healthy children. They had no hepatomegaly, they were of average weight and height, and clinically nothing



Text-fig. 10. Protein intake of fifteen Jamaican children: ten with hepatomegaly, five apparently healthy controls. Clear areas: total protein; shaded areas: animal protein. Intakes expressed as percentage standard requirement (3·5 g. kg.). Reproduced by courtesy of the editor, *British Journal of Nutrition*.

abnormal was detected. The last ten children were selected from welfare clinics, and their only abnormal sign was a firm or hard liver with a sharp lower edge. Whilst the whole series obviously had too little protein compared with standard requirement, the children with liver enlargement had much less total protein and less animal protein than the healthy group. The healthy children also had more sources of animal protein as well as larger quantities; they had an average of 3·2 different sources of animal protein, as compared with 1·3 in the children with hepatomegaly. There was also a distinct difference in the pattern of cereal intake. The healthy group received more valuable cereals, such as whole wheat, oatmeal and brown bread while the other group, with liver enlargement, had white bread and corn-starch. There is, therefore, a difference in the quantity of animal protein and in the quality of vegetable protein.

Dr Stuart also mentioned something about the presence of preceding infections in cases of V.O.D. It often appeared that the onset of acute V.O.D. was precipitated by a preceding non-specific illness, commonly a childhood infection such as pertussis.

I have tried to correlate protein deficiency in the diet with the severity of the preceding infections. I divided the diets into three groups: diet A was a fairly good diet, deficient in protein but not severely so; diet B was poor and diet C very poor. Diet B was most commonly found; it amounted to half a pint of milk a day and cornmeal porridge. Children on diet C had corn-starch or arrowroot porridge with little or no milk at all.

Table 12 shows a series of cases of acute V.O.D.; over half of them gave a clear history of an illness preceding the onset of V.O.D. In some it was severe, such as pneumonia, pertussis, broncho-pneumonia or tuberculosis; others had mild colds and coughs.

Only four cases had a fairly good A diet. Three of them were of standard weight and all three had a very severe illness, broncho-pneumonia in two and tuberculosis in one. The fourth was 32% under weight and gave a history of a cold with fever immediately preceding the onset of acute V.O.D.

Of the nineteen children on the poor B diet, those who were more or less of standard weight had severe infections, but those who were under weight usually had a mild preceding illness; sometimes there was no history of infection, but an illness may have occurred which had escaped notice. In nineteen children on diet C, the very poor diet, the same thing can be seen. In the under-weight children there was usually evidence of only a minor preceding illness.

From these facts I think there may be an inverse relationship between the diet and the severity of infection necessary to precipitate acute V.O.D. That is, any non-specific toxin may possibly precipitate the acute disease in a protein-deficient child.

FREMONT-SMITH: It seems to me, Dr Dean, that if you are going to demand proof of protein malnutrition in these cases of V.O.D. you must also demand it in the others—the cases of kwashiorkor. As I understand the situation, the hypothesis of protein malnutrition in kwashiorkor, fertile though it looks, has not yet been proved in terms of either qualitative or quantitative depletion of protein. Am I wrong?

RAO: Dr Dean has raised a very formidable question, and I am not here to advocate the case of Dr Bras. When we are trying to define what is protein malnutrition I think we must take all the available data, clinical,

Table 12. *Relationship between diet and infection in acute venous occlusive disease*

Diet A (fair diet)

Cases	1	2	3	4
Percentage under weight	.	.	.	32
Previous infections ↗ mild	0	0	0	+
↘ severe	+	+	+	0

Diet B (poor diet)

Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Percentage under weight	.	.	.	.	.	.	.	.	.	11	14	17	17	19	22	22	23	28	35
Previous infections ↗ mild	0	0	0	0	+	+	+	+	0	0	0	0	0	+	+	0	+	0	0
↘ severe	+	+	+	+	0	0	0	0	0	0	0	+	0	0	0	0	0	0	0

Diet C (very poor diet)

Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Percentage under weight	.	.	.	.	.	11	14	15	15	16	18	20	20	26	27	30	31	34	37
Previous infections ↗ mild	0	0	0	0	0	0	0	0	0	0	0	+	0	+	0	0	0	0	0
↘ severe	+	+	0	0	0	+	+	0	0	0	+	0	0	0	0	0	0	0	0

biochemical, pathological and histological. It is but right that we present the data which we have, and try to analyse how far they fit the accepted picture.

The question of infantile cirrhosis is related, at least from the description that Dr Bras has given, to malnutrition. It is for us to study and analyse whether there are superimposed factors like toxins, poisons, or anything else. There is no doubt that infantile cirrhosis exists, but 'cirrhosis' is often a very loosely used term, as opposed to fibrosis. Cirrhosis is defined as a diffuse degenerative hepatitis and replacement fibrosis associated with pseudolobulation. Those are the three postulates, as it were, for the histologist to say that this is cirrhosis.

With this background, I shall show you the histology of infantile cirrhosis as we see it in India. I shall confine my remarks to the histological aspects and at a later stage, at the clinical meeting, I shall deal with the clinical features. This will be a sort of representative group of what we call infantile cirrhosis.

Pl. 10 (1) shows a normal liver stained by a modification of Foot and Menard's(22) silver impregnation technique. By this method the parenchyma is completely dissolved, and only the reticulum is well brought out. This fine reticular network forms a beautiful pattern, which remains the same from whatever part of the organ you take the tissue.

In contrast to that, Pl. 10 (2) is from a typical case of infantile cirrhosis, where you find that there is a thickening of the central veins. The reason why I bring this out is that Dr Bras described a similar condition. The end-results were the same, but the beginning is quite different. In the case of infantile cirrhosis, from the study of a number of biopsies, we found that the earliest lesion is a necrosis or death of the parenchymal cells around the central vein. That is where it differs from the histological findings in the Jamaican cases. After the necrosis the reticulum undergoes a sort of structural change. There is collapse and condensation of the reticulum and, at a later stage, thickening (sclerosis). Therefore there are two different types of change taking place, which result in the development of the fibrotic process. In most of the Jamaican cases, if I have heard correctly, there is no necrosis of the parenchyma. Is that correct?

BRAS: Correct.

RAO: But in this particular case, this is exactly what we get in the experimental animal, if you deprive it of protein. One of the changes is a necrosis, and sometimes it will be massive and sometimes it will be local. We definitely know now from experimental work that protein deficiency can result in two lesions—one a pure fatty change and the other a necrosis of the hepatic parenchyma. Both these two types of lesions may ultimately result in fibrosis, but the beginning is quite different. Unfortunately, the morbid histologist is at a disadvantage, because he is usually able to study only the terminal lesions. But that is where the experimental histologist comes in. He tries to study the earlier changes. Perhaps it is like boring a tunnel in a big hill; both can work from opposite ends, and they might meet somewhere in the centre.

My human material is thus confined to the histology of the later stages. Pl. 10 (3) shows one of the criteria I mentioned of a typical cirrhosis, a very fine lobulation. I do not call it monolobular or unilobular, since these older terms are no longer accepted.

MACKAY: Does the necrosis of the parenchyma come before the vascular changes or after?

RAO: Before. The first change is necrosis of the parenchyma around the central vein.

GYORGY: Dr Rao, a slight correction: the animal which gets necrosis is not only deprived of protein, but also of vitamin E.

RAO: Yes.

WATERLOW: Dr Rao, would you not agree that this centrolobular thickening of the reticulum is a fairly non-specific finding? For instance, it may occur in gross anaemia.

RAO: That is why I started by saying that the changes observed must satisfy all the criteria. In the case of cardiac fibrosis there is thickening of the central vein and fibrosis, but it is never a cirrhosis. Fibrosis is confined to the area around the central vein. You will never find this pattern of radiating fibrous tissue and the pseudolobulation I have just shown you, which is seen in cases of infantile cirrhosis. The condition is entirely different from the histological point of view.

Here we postulate a replacement fibrosis, following death of the parenchymal cells. Subsequently the reticulum collapses; there is condensation and thickening, and then the fibrosis starts.

HILL: You have actually seen necrosis of the parenchyma? You are going to show it?

RAO: That is from biopsies. Unfortunately, we have not been able to get all the material.

HILL: I disagree a little with your remarks about the changes which follow congestion. You do get a lot of fibrous tissue round the centrolobular vein, which can radiate out in a most irregular pattern.

RAO: I agree, but rarely do you find any attempts at pseudolobulation or a uniform pattern. The pattern is entirely different in the case of cardiac fibrosis. In infantile cirrhosis there is necrosis and a good deal of regeneration of liver cells. This means that there is an attempt at lobulation, but the child dies long before the pseudolobules can really form and function effectively. Therefore the lobules are very small.

During the discussion I asked Dr Bras whether there was jaundice in his cases. One of the main clinical features of infantile cirrhosis in India is that jaundice occurs fairly early (23); it deepens and the child dies in a state of cholaemia. When we see the terminal stage in the liver, you will find that there are biliary thrombi in many of these parenchymal cells. Pl. 10 (4) is a high-power micrograph to show these thrombi; clinically, also, you find jaundice.

Whether or not this condition is related to protein malnutrition it is for us to judge. In the experimental animal you can produce a similar lesion by dietary means but unfortunately we do not get any changes in the central vein. This raises the question whether our cases present the same picture as those of Dr Bras. There are certain similarities, but there are also a number of discrepancies.

One of the differences is that at no time do you find necrosis of the hepatic parenchyma in the cases presented by Dr Bras. That raises a doubt, which Dr Dean has very rightly pointed out, whether this is the result of malnutrition. Moreover, in the sections which Dr Bras has shown there is oedema in the subintimal spaces; this is very rarely found either in man or in any experimental animal. That again raises the doubt whether there are any other superimposed factors, apart from malnutrition, such as toxins or poisons in the cases of infantile cirrhosis which he presented. Although it is not obviously relevant to the problem of protein malnutrition, I think it is worth while discussing what exactly is the condition, and then whether it has any bearing on the problems which we are studying.

AYKROYD: Do all your cases die?

RAO: Invariably, if they are not treated. They occur mostly in vegetarians. 'Vegetarianism' is a very peculiar term. The people are really lacto-vegetarians, not ovo-vegetarians, because they won't even eat eggs. There is no doubt that the diet of these children is very poor, especially in proteins of the animal variety. Whether that has a bearing on our present problem is a point worth consideration. The fact that the disease is found in only a few countries does not prove that it is not related to malnutrition. Malnutrition exists in India. We have a condition similar to kwashiorkor, and we also have this other condition which is histologically different. Ten years later, we may put two and two together and say: 'Well, we made a mistake 10 years ago; now we are correcting our mistake.'

GYORGY: Do you have proliferation of the bile ducts?

RAO: This condition was originally described as infantile 'biliary' cirrhosis. Now we know that this is wrong because you seldom find that the biliary ducts are affected—either the small or the large ducts—except in the terminal stages, where there is occlusion of the very fine bile ducts. That is probably the terminal stage.

GYORGY: But there is no proliferation?

RAO: No.

BRAS: You have not brought out in this presentation (although you did so in your original paper) your opinion that the venous occlusion was a pivotal thing for the development of the cirrhosis afterwards. Are you still of that opinion?

RAO: Yes. I am a little nervous about developing this point further. Because this is more or less an offshoot of the main discussion, I thought it better to put forward only the fundamentals. As pathologists, I think we can argue for days as to which change comes first. There is no doubt that in these cases the changes in the central vein are of importance, whether it is in a child or an adult. In the case of the so-called toxic cirrhosis, where you find big nodules of regeneration, you will find the same changes in the hepatic venous tree, but not in the fine terminals, only in the larger veins. Therefore there is no doubt that the hepatic venous tree is very closely connected with toxic cirrhosis. In the case of portal cirrhosis, again, you will find many changes around the portal veins, not round the hepatic venous tree. Why? That is a question which the pathologists must answer at some time.

MACKAY: It seems to me that there is no generalized vascular change in the body as a whole. What vascular lesions you see are isolated in the liver. Therefore it would seem that to some extent it is a parenchymal change and not a vascular change which starts the story. If it were a vascular phenomenon, you would expect to find it generalized, probably followed by degenerative changes in other cells.

RAO: I prefaced my remarks by saying that the fundamental change is in the parenchyma. The early changes are necrosis or death of the parenchymal cells. Whether it is haemorrhagic necrosis or something else is a point which the pathologists must decide. The changes in the hepatic venous tree occur at a later stage. Therefore, I think the material which was presented by Dr Bras may have given rise to some sort of misunderstanding, because he has put the emphasis on the venous tree.

HILL: Dr Rao, I am unhappy about this, because you haven't shown us anything that would prove the case for necrosis of the parenchyma. You have shown us end results. The patients always die, but from what? From necrosis or fibrosis?

RAO: They die in a state of cholaemia. Side by side, you have evidence that there is necrosis of the parenchymal cells, and attempts at regeneration.

They are in balance. There is also fibroid induration, and the child dies of cholaemia due to functional failure of the liver.

HILL: My point is this, that at some stage in the pathogenesis of this disease, you must have only necrosis in the liver. What you showed us were late results.

RAO: I said that I was showing you one of the end stages, but in experimental material I could show you the genesis of a very similar lesion.

HILL: But have you seen biopsies of patients with nothing but necrosis in the centre of the lobule?

RAO: Yes, we have seen a number of cases. At Mysore, one of the places where this disease is quite common, we have for a long time been investigating the earlier changes in the liver. A number of biopsies were done at different stages, and at no stage did we find a fatty change in the parenchymal cells. In the beginning, in the biopsy material that we have seen, the first change was necrosis of the liver cells around the central vein. That is exactly similar to what we find in the experimental animal if you deprive it of protein and, as my friend Dr Gyorgy has said, of vitamin E.

HILL: And that means complete dissolution of the cell, with haemorrhage, followed by iron positive staining later on?

RAO: Yes.

BRAS: When you said 'haemorrhage' in this context, Dr Rao, does it look like the things I have shown and termed 'blood lagoons'?

RAO: No, that is quite different.

MACKAY: It seems that Dr Bras does conflict with Dr Rao. Dr Bras has shown us sections in which the vascular changes seem to be paramount. How do you know, Dr Bras, that there is nothing wrong with the liver cells?

BRAS: I do not pretend that there is nothing wrong with the liver cells. I have not said that either. I have only said that I have not seen a morphological change in the liver cells which pointed to necrosis or to any large-scale degeneration. I could not see any evidence which indicated that damage to liver cells had preceded the vascular changes.

SÉNÉCAL: What age were the Indian cases?

RAO: The same age at which so-called kwashiorkor is seen, that is, between the ages of 9 months and 3 years. Therefore they occur in the age period predisposed to protein malnutrition. The dietary history is certainly in favour of protein malnutrition. Whether or not the histological picture fits into this, we have to decide.

HILL: The jaundice is associated in your mind with the necrosis; is that right?

RAO: Jaundice is found in the later stages, not in the earlier stages.

DEAN: Dr Rao, I think, in your earlier description of this disease [illegible] you referred to a specific religious group with specific dietary habits. Are you still seeing cases only in that group, or are many different groups of people involved?

Rao: I have not changed much from what I published earlier. You see, we have two types of case among children who are malnourished. One is the cirrhosis which I have just now described, and in the other, which is a slightly older group, you get the same picture as in Laennec's cirrhosis. That is why I am tempted to believe that protein deficiency can produce two types of lesion. Why it does, when it does, and how it does, we have still to decide.

Williams: How much milk are these children getting? Is it mother's milk or cow's milk?

Rao: Most cases have been weaned from mother's milk, and although there is no taboo about drinking milk from cows, when they are weaned they are put on a very poor diet, consisting mostly of very soft cooked rice and sometimes pepper-water.

At this stage, however, I only want to point out the histological lesion in children in whom, presumably, there is a deficiency of protein in the diet. To summarize, there is a typical lesion which, from the experimental point of view, simulates a toxic necrosis with subsequent fibrosis. 'Toxic' is used in a very loose way, to implicate not necessarily poisons alone; the lesion may be metabolic, it may be dietary.

Bras: Dr Rao, talking about toxins, could you possibly clarify one point? Dr Gyorgy and I have conflicting reports on the use of castor oil in this particular group of children. Would you tell us something about the possibility of repeated purgation with castor oil, as being possibly involved in the aetiology of this condition you are describing?

Rao: There have been a number of conflicting reports, that children who are given castor oil from birth develop infantile cirrhosis. You see this disease in children who are soaked in castor oil, and by soaked I mean the whole body covered with it, castor oil inside and castor oil outside. But there are a number of children to whom castor oil was not given and who still have the disease. From the epidemiological point of view I think that is quite enough evidence to show that castor oil is not incriminated. You might equally say that because they are getting breast-milk they get this disease!

Santos: We use castor oil widely in Brazil and we have not seen cirrhosis in malnourished children.

Aykroyd: I want to ask Dr Gopalan a question because he has been working in South India, whereas Dr Rao has been working in Bombay. Has there been any change in Madras in the incidence of this particular condition, which was very common in my time in India? You may have had some recent contact with that aspect of it.

GOPALAN: No, sir. I was going to say that I find it very difficult to believe, just by studying the incidence of this disease as it occurs in India, that protein malnutrition could have anything much to do with it. In Coonoor, where we see large numbers of cases of kwashiorkor, infantile cirrhosis is practically non-existent. We get this condition in the socio-economic group in which kwashiorkor is unknown. If protein malnutrition plays any part at all in infantile cirrhosis, I find it very difficult to understand why it should be so extremely uncommon in those groups in which kwashiorkor is so common.

I do not know much about infantile cirrhosis, coming, as I do, from Coonoor, where we do not see the cases, but I have discussed this problem with Dr Achar, who is a paediatrician in Madras and deals with these cases in large numbers; I think that the present trend, as far as his results go—though I wouldn't like to pit myself against Dr Rao, with his experience on the subject—seems to be that we are dealing with a virus disease.

As far as the incidence is concerned, answering your question, Dr Aykroyd, it still continues to occur in what I would call the well-to-do classes. They are not all vegetarians. Perhaps they do not have a well-balanced diet, but I don't think the diet of these children could be called grossly inadequate.

Therefore, my own personal view—and I know that Dr Rao does not agree with me on this—is that infantile cirrhosis, as we see it in India, is probably not a manifestation of malnutrition.

BRAS: Do you also mean to say that malnutrition does not condition the liver and make it more prone or more susceptible to a virus disease?

GOPALAN: That is a very difficult question to answer, but I think, as far as virus diseases go, malnutrition plays a very small part.

CLEMENTS: If anything, it plays the opposite role?

GOPALAN: Yes, I think the evidence is to that effect.

BRAS: No, I would like to take you up on that question, because I believe that the mortality of virus hepatitis in Ceylon, as reported by Professor Fernando (24), is about a hundred times as high as the figures for the United States and for Western Europe. This cannot be ascribed to a difference in virulence; in fact, I believe it has been accepted by most workers as being the result of a conditioning of the liver and of the body as a whole by malnutrition, before the onset of the virus infection.

GOPALAN: No, there are two factors there. I think there is some work on this aspect among the troops in the Middle East. The susceptibility is somewhat less in malnourished subjects, but once they get the infection, the mortality is very much greater.

Bras: The idea we are driving at in Jamaica is this: that there may be a conditioning of the liver by malnutrition or protein undernutrition, on top of which there is another factor. Thus we are thinking very much along the line of a double aetiology, as many people have thought in other parts of the world about the cause of cirrhosis, infantile as well as adult.

Gopalan: The only point I wish to make here is that kwashiorkor, as we understand it in India, and infantile cirrhosis are very far apart from the point of view of incidence. Going by the incidence and going also by the response to high protein treatment, I find it very difficult to believe that in infantile biliary cirrhosis we are dealing with a manifestation of protein malnutrition. I should rather take the view that it is, perhaps, the result of a virus infection.

Gyorgy: Why do you have it in only one social class?

Gopalan: That is very difficult to say. I don't know the answer. There is a peculiar familial incidence also. There are children in the same family who get it again and again. Of course, one would argue that probably it is because they are given the same diet.

Williams: I should like to emphasize the point that differences in diet condition people to different reactions to diseases. I think it is obvious; it happens with every known disease. Another thing that is very important is the source of the milk. I don't know if you have done many analyses of milk, but many of the mothers of these children are malnourished, and very often the milk is from a malnourished cow. I have seen cases of infantile cirrhosis in India which were getting plenty of milk protein, but the cows were deplorable as examples of cows. We are all talking about proteins as if there was only one kind of protein.

Clements: But have we any evidence that the malnourished cow will produce an inferior milk?

Williams: I am asking that question.

Rao: We are carrying on certain experiments on mothers to find out not only the quantity but also the quality of the milk, and whether there is any difference in the amino-acid composition of the milk. Recently one of the workers in my department has shown from experiments that there are certain amino acids which are missing in human milk from malnourished mothers.

It is always easy to say 'virus'. We always use viruses to explain things to our students. But there is no evidence to prove, at present, that infantile cirrhosis results from a virus infection. Unlike what you get in infective hepatitis, it is limited to certain families, with no contact to bring in the disease, and it is, no doubt, familial. The diet is monotonous and deficient. Whether or not the disease is related to protein deficiency is a point which we must investigate; I, for one, will not dogmatize or emphasize anything at this stage, except to draw your attention to three facts: that there is a deficiency in the mother's milk, there is a deficiency in the children's diet, and the histologic picture is one of hepatic damage, similar to that which we find in the protein-depleted animal.

BRAS: As one approach to the problem of the cause of the fibrosis in our cases I have recently published a table in which are put down some particulars about occlusion of the hepatic veins, which is called by some people the Chiari syndrome and by other people, mainly European writers, endophlebitis obliterans hepatica(25). The nature of the lesion has been variously interpreted as inflammatory, degenerative, due to congenital anomalies, or to thrombosis; this in turn may be either primary or secondary to other processes in the liver or vena cava.

I want to call your attention to the fact that the condition has been seen in humans who had accidentally ingested *Senecio*(26);* it has also been reproduced in animals with *Senecio*, and it was quite obvious from these experiments that general undernutrition of the animals enhanced the effects.

I also think it relevant to bring in here the point repeatedly made by Maegraith and his collaborators(27), that constriction of the hepatic venous tree takes place under a variety of circumstances, such as blackwater fever, but also in all sorts of trivial diseases; that, furthermore, in experimental animals this hepatic venous tree has proved to be very prone to damage by alkaloids from various sources, the senecio alkaloids being one example. It would appear from this that occlusion of the hepatic venous tree from swelling of the intima, and perhaps from other changes like spasm (which I have not been able to demonstrate, although I find evidence suggestive of it) seems to be able to develop after a host of aetiological factors, in man as well as in the experimental animal. Whether to call this condition endophlebitis obliterans hepatica or veno-occlusive disease is a matter which we can go into later.

As a side issue, I would like to refer to many discussions that have been going on in the Macy conferences on the problem of the regulation of the blood flow through the liver(28). We have evidence, from the beautiful experiments of Dr Knisely(29) that in frogs there is a valve mechanism situated at the point where the sinusoids bring the blood into the central space (a term advocated by Elias). We also know from other studies that contraction of the muscles of the hepatic veins occurs. Then we have the concept which was developed by Deysach(30), who speaks about 'sluice channels'.

It is quite certain, from physiological experiments (Krogh & Lindhart(31)) that such a regulating mechanism must exist in the human liver. Although I am not aware of any definite observation in humans to prove where this regulating mechanism in the liver is, I have been toying with the idea that swelling of the intima is a possible constituent of such a regulation. I have a number of major objections to it myself, one of them being that I cannot very well visualize why a pathological state should occur if the mechanism is a physiological one for regulating blood flow. It seems that this condition, which we have actually seen in our children, is largely, if not entirely, reversible; it seems to be able to come and go quickly, with or without residual changes. There are many children who have this condition and who, in the second biopsy, do not show any residue at all, either in the veins themselves or in the surrounding area. Admittedly, these were only biopsies—small samples of the liver—but they were, nevertheless, suggestive.

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* Common name: ragwort.

STUART: I would like to confirm that. Clinically, many of these patients recover completely, and hepatic enlargement does not recur, so it does fit in with the histological recovery that Dr Bras points out.

BRAS: Leaving this side issue for the moment and continuing with the aetiology, I have been very much impressed with the clinical observation that these children are definitely undernourished. The data which Dr Rhodes has collected on these patients support that fact. I have also been impressed by the biochemical data, which point in the same direction. So have other Jamaican workers before me. Professor Hill and his group have very clearly drawn attention to the fact that these children cannot be called 'normal' Jamaican children, but that they are definitely subnormal. Earlier investigators, such as McFarlane & Branday (17), and Royes (18), have already drawn attention to the fact that bush teas—I know I am flogging a tired horse—are given in very large amounts here in Jamaica. It has been very interesting for me to demonstrate now in the liver a condition which is known to occur in experimental animals given bush teas, so to speak, or given alkaloids. It was also very intriguing to learn from the experimental work that, if these animals were undernourished, the changes were much more prone to occur.

We do not know much about the aetiology. We only think that it lies somewhere in a factor A superimposed upon a factor B. We firmly believe that there is a conditioning of the liver through protein undernutrition, on top of which a factor B probably acts, resulting in this condition. That is as far as our thoughts go now. We have no proof for this, except for the circumstantial evidence which I have already mentioned.

MACKAY: Does the liver change very much in size and very rapidly in the living child? When you feel a liver in a child today, is it possible to find that in the same child it will not be palpable the next day?

Stuart: Yes.

Mackay: Such rapid changes in volume are likely to be due to a change of blood volume in the liver. Burn (32) maintains that there is contractile tissue at the point where the liver sinusoids empty into the intralobular vein. When these elements contract there is a marked swelling of the liver. I wonder if it is at all possible that some of these substances, such as the *Senecio* which you are talking about, have a pharmacological action of this nature, and that they are constantly attacking the liver, producing a congestion and then other changes?

Hill: Dr Rhodes and my colleagues and I have studied this clinical and pathological condition for some time, and we called it 'serous hepatosis' (11). I would like to emphasize that clinically and pathologically serous hepatosis is identical with veno-occlusive disease. If I were to show any slides, they would be exactly the same as Dr Bras's. In point of fact, what we missed is the venous occlusion, which is quite clear, as far as I can now see, in our series of cases.

Bras: The next type of liver disease which we frequently see in Jamaica and which is related to malnutrition, is kwashiorkor. If I adhere to the principle that Dr Waterlow initiated yesterday, to get clear first what we are talking about, the next question would be, what is kwashiorkor? We are all familiar with the criteria laid down for kwashiorkor by Brock & Autret (33); the clinicians here agree that the full-blown picture is relatively seldom seen in Jamaica. The children whom we do see show certain signs, which Dr Stuart or Dr Rhodes might tell us.

Stuart: In brief, the typical Jamaican kwashiorkor is this: the common age of onset is about 1 year. There is generally a history of anorexia and sudden swelling due to oedema. Diarrhoea and steatorrhoea are not prominent features. There is often red hair but not always. The subcutaneous fat is usually plentiful in our cases, and hence the common picture we see is the 'sugar baby' type—what we call 'blubbery' kwashiorkor. The skin changes are usually not marked, and dermatosis is rare, though it does sometimes occur. Mucosal lesions are often not present. The fat of the liver is markedly increased. We invariably find very low serum proteins and very low plasma cholinesterase. The average plasma cholinesterase in our cases is 0·26 Michel unit. Finally, there is always hepatomegaly.

Clements: I think that we could summarize and say that the definite clinical signs are a history of poor diet, anorexia, hepatomegaly, the presence of subcutaneous fat and oedema.

Gyorgy: You said there is much subcutaneous fat; how can you be sure about that?

Stuart: I will show you a typical case and let you judge.

RHODES: I would like to disagree with one point Dr Stuart has made, because I feel it presents an erroneous impression of kwashiorkor in Jamaica. I don't believe that the typical case is fat and blubbery. I have studied in detail only twenty-three cases of kwashiorkor, but every one of those cases was wasted to a marked degree, although some subcutaneous fat was always present. I hope later to have an opportunity to show you the weights of these cases; they were all from 40 to 50% underweight.

WATERLOW: I don't think there is really any difference between Dr Rhodes, Dr Stuart and myself. We all agree that these cases are 40–50% under weight, and when we say 'fat', we mean fat relatively, compared with marasmus. I was struck years ago by the fact, first of all, that as far as one can judge clinically, there is gross muscular wasting, and secondly, that there are fat depots left which you can detect clinically; you can see them post-mortem if you put in a knife, particularly in certain sites—in the adductor regions of the thighs, the cheeks, and the legs, whereas there is gross wasting in the axilla and over the trunk (34). I think, therefore, that when we say 'fat', we mean compared with a starved baby, not compared with a normal baby.

BRAS: I would like to give you a cross-section of the histological findings in thirty-nine cases which were recently reviewed by Dr Jelliffe, Dr Stuart and myself (35), of which eighteen were cases diagnosed by the paediatricians as kwashiorkor, thirteen were called marasmic kwashiorkor, and eight were considered clinically to be marasmus.

STUART: May I first show one picture to illustrate these two clinical types that we differentiate? These are two children within 2 months of each other in age (Pl. 11). One is 10 months, on the left-hand side (A), and the other is 12 months, on the right (B). On the left is the blubbery type that I described just now.

AYKROYD: That is your 'sugar baby'?

STUART: Yes. The other one, on the right, is what we call marasmic kwashiorkor.

BRAS: Now, I have a failure to report: that is, I cannot find a reliable morphological criterion to differentiate a case which is clinically kwashiorkor from one which is clinically marasmus. I only see differences in degree of fatty change, no differences in the process as such. I hope that somebody can convince me that I have been very foolish. I would like very much to learn something about this.

I judged the fat by grading it from 1-plus to 3-plus for various parts of the lobule—the periphery, the midzone, and the central area. Dr Waterlow and I have found, in comparing the histology with the biochemistry, that our findings roughly correspond, except that there is a tendency in the histological sections for small amounts of fat to be overestimated and large amounts to be underestimated. By this histological assessment the result was that the kwashiorkor group had the most fat, the marasmic kwashiorkor group came next, and the cases of pure marasmus had the least fat. The localization was predominantly in the periphery and the midzone of the lobule. The fat, as we saw it most of the time, occupied the greater part of the cells, and small vacuoles were seen only in follow-up biopsies, when the fat was receding.

We also saw lipodiastemata, a term which has been used by Dr Hartroft (20). These develop when the membranes, which as Dr Waterlow pointed out yesterday, can be extremely thin, disappear between neighbouring cells, which then coalesce. As Dr Hartroft has described in serial sections, these lipodiastemata, or fatty cysts, may show as many as eighteen nuclei, so it seems that at least as many cells must have taken part in the formation of such a cyst. We never saw such extreme cases. We have seen, of course, fusion of cells into larger vacuoles; these, in our opinion, seem to occur in direct proportion to the total amount of fat. It has been difficult to judge whether, under treatment, such a fatty cyst would give up the fat less readily than a normal, non-ruptured liver cell would, as Dr Hartroft has shown.

Necrosis of the liver cell, as usually reported, is absent from the fatty liver. I have been able to demonstrate some necrosis without noticeable predilection for any part of the lobule, but it was always very slight—for instance, something like two or three necrotic cells per section.

During treatment in hospital the fat disappears from some cells quicker than it does from others. This has been a point of frequent discussion between Dr Waterlow and myself. Why is it that the fat disappears more readily from certain cells? What is it that keeps the residual fat, as we like to call it, in the other cells? Is there a morphological criterion by which we can recognize a cell which will less readily give up fat from one which will give it up readily? If we only had such a criterion, then it would be a good guide for prognosis.

That is the second failure which I have to report to you regarding these slides. The morphology of the liver cell does not tell us anything much about the prognosis. Of course, it is of value in the follow-up biopsy that we see a reduction in the amount of fat, but by this time the paediatrician already knows, from other clinical signs, that the patient is doing well. As far as I can see, I myself have been of no help to the clinician except in pointing out that in a particular patient the fat evidently was disappearing rapidly and that the patient is at least reponding to treatment.

The amount of fat, which Dr Waterlow discussed yesterday, is another failure. I have not been able, so far, to correlate the amount of fat that I see histologically with the condition of the patient. I warned you that the story would be one of inefficiency and unexplained difficulties.

Pl. 1 shows the type of liver which is frequently seen, and to which Dr Waterlow was alluding yesterday. You see that the cell membranes may be extremely thin, and even may not be present at all. There may be some doubt whether or not the rupture is an artefact occurring in the process of the section cutting, but I don't believe it is in all instances.

Hill: Dr Waterlow said yesterday that an artefact sometimes will imply that there is something wrong *in vivo*.

Bras: Exactly. I also saw structures like this, Pl. 12 (1), though not often, where it seemed to me that cells had coalesced into large cavities with 'extracellular fat'. You can see, incidentally, that not all the liver cells are fatty in this case. I also want to draw your attention to the fact that in these pictures you will frequently see cytoplasm which does not look normal. That is a common occurrence in our cases, although I do not know what significance to give to the various cytoplasmic changes. Rarefaction of the cytoplasm is very often seen.

Autret: This is all biopsy material?

Bras: Yes, they are all biopsies that I am going to show you now.

Often during recovery we see an increased activity of cells inside the sinusoids (Pls. 12 (2) and 13 (1)). These cells are frequently of the reticulo-endothelial variety, but we also see many lymphocytes and occasionally eosinophils; we have never seen as many lymphocytes as in the cases which Dr Davies (37) described, and which he found almost to resemble leucaemia.

Pl. 13 (2) shows a thing which has been described before, the perilobular reticulin increase. Notice, as has been described, that there is frequently a thickening of pre-existing fibres, and possibly here and there a little actual increase in the number of fibres as well.

Another phenomenon which we see frequently is nuclear vacuolation, Pl. 13 (3), usually located close to the portal zone, or in the portal area; these are commonly described as glycogen vacuoles (38). Most of them are periodic-acid/Schiff-positive.

The nuclear changes were very interesting to me. We have seen a variety of them, in kwashiorkor, in V.O.D., and to a much lesser extent in our control group. Polyploidy of the nucleus is a common thing in these children, the number of binucleates also being larger than one might expect in the normal liver of a child of this age.

Other changes in the liver include amitotic nuclear fission and mitosis (Pls. 14 and 15).

Sénécal: At what time in the evolution do you see this?

Bras: At all stages.

Sénécal: At the beginning or after treatment?

Bras: All biopsies are taken after some amount of treatment. I see the nuclear changes in the first biopsy but, as you will realize, in the fully fatty liver the nucleus is pushed over to the side and it is very difficult to evaluate nuclear changes in that stage. When the cell has recovered some of its cytoplasm the nucleus can be better seen, and it is at that stage that I have made most of my observations, as you can judge from the pictures; so we have seen them best, on the whole, when the child was recovering.

Here, Pl. 16, is the condition of cellular degeneration that I was talking about before. There is an eosinophilic change of the cytoplasm; the nucleus is sometimes small, pycnotic, fragmented or altogether absent.

Gyorgy: I might say for the record that such single-cellular necrotic changes can be seen regularly in animals on a diet which produces a fatty liver and is relatively low in protein.

Bras: Yes. That is an interesting point connected with this, which will come up later in relation to the after-effects of kwashiorkor. Do you think, in your experimental animals, that the cell necrosis which you see is of any importance in producing post-necrotic scarring?

Gyorgy: There is no post-necrotic scarring in the fatty liver, but I think it is very important for the development of cirrhosis.

Waterlow: I have begun to wonder, from my chemical measurements, if there might not be a loss of nuclear nucleic acid in fatal cases. The amounts are low. Would the histology possibly bear that out—the nuclei being destroyed and disappearing?

Bras: It may be that in fatal cases more of the nuclei have been chromatolysed. I have not estimated the relative number of cells which do not show a nucleus.

Another thing which we have seen, though only in two cases so far, is pigment (Pl. 17). I don't think it is malaria pigment, although Dr Waterlow thinks it might be.

Gyorgy: Is it ceroid?

Bras: It is not ceroid. It is less acid-fast and less sudanophilic than ceroid would be in the paraffin section. I have no frozen sections. In my opinion it is lipofuscin.

Mackay: Are there any changes in the relationship of the size of the nuclei to the cell mass as a whole?

Bras: Yes, of course there are, because the fatty cell is swollen, but I have not measured either the nuclei or the cytoplasm.

Mackay: Apart from the fat, don't you think it might be of value to do a quantitative study? I had occasion to do this some years ago in work on the pancreas, and I found that the only way I could really get an answer was to do a planimetric measurement. Has anything been done on these lines in the liver?

BRAS: It has been a matter of frequent discussion between Dr Waterlow, Dr Rhodes and myself, but we have not been able to find the time to do anything of the kind as yet.

WATERLOW: If you do it at all, you have to do it very laboriously and very accurately.

DEAN: The series of slides which you showed, Dr Bras, the second series, were from marasmic kwashiorkor, kwashiorkor, and marasmus?

BRAS: Yes.

DEAN: And were the first ones kwashiorkor and the last ones marasmus, or were they not in order?

BRAS: As I said at the beginning, I made a cross-section. I have not endeavoured to give them to you in any specific order. The reason is that, since this is a conference in which every single participant probably knows more about kwashiorkor than I do, I felt it would be boring to give the classical picture of kwashiorkor and marasmus, as it is well documented and known to everyone. Therefore I presented a cross-section of the things which had struck me as being both extraordinary and interesting. That was my approach to the selection of the slides. I even included slides from children who, as I said in the beginning, were in the non-hepatic group. Is this answer satisfactory to you, Dr Dean, or can I help you a bit more?

DEAN: I'm sorry, no. I am rather bewildered when I see that I have in fact not been looking at kwashiorkor, as I thought, but at a number of different conditions. I obviously haven't got the right approach.

BRAS: I was trying to make clear from the beginning that I have no morphological criteria which demonstrate principal differences between one disease and the other.

FREMONT-SMITH: That is the reason why you put them all together, not that you didn't want to show us the different types, but because in your own group of cases, you did not find any differences? Is that what you are trying to say?

BRAS: I also took it for granted that everybody knew what a fatty liver looked like in the advanced classical case of kwashiorkor, as published so many times.

SCRIMSHAW: Have your clinical cases included really extreme marasmus, extreme cachexia? The picture Dr Stuart showed (Pl. 11) is not nearly as severe as we commonly see in Central America. Do you have in your series maximal cachexia or maximal marasmus?

Stuart: We have. That photograph was a case of marasmic kwashiorkor, but Dr Bras's material does include cases of extreme marasmus.

Gyorgy: May I ask you a kind of examination question? What are your criteria for excessive marasmus?

Stuart: When a child is so thin that in my opinion it cannot get any thinner.

Gyorgy: No, no, that is not the criterion. The criterion is complete loss of Bichat's fat pad. Do you have that?

Stuart: I didn't look for it.

Gyorgy: Well, that is the only sure criterion.

Fremont-Smith: Didn't you say, or did I misunderstand you, that in the group which you have examined you did not find any morphological distinctions between the different clinical types of case? That is, you did not find morphological distinctions between marasmus, marasmic kwashiorkor, and kwashiorkor, and that was the reason why you gave us a cross-section of the whole group. Is that a fair statement?

Bras: I said, in actual fact, that I did not know any reliable morphological criteria which enabled me to differentiate, or to say in a specific case: 'this must come from a marasmic child' or 'this must come from a kwashiorkor child'.

Dean: Except that the amount of fat tends to be very great in kwashiorkor and very small in marasmus.

Bras: That's right.

Hill: When you have extreme marasmus, have you found no fat in the liver?

Bras: I have always been able to find at least small amounts.

Waterlow: According to my measurements, some of the marasmic cases have no excess of fat in the liver.

Gyorgy: Chemically? quantitatively?

Waterlow: Yes. I feel that the specific thing in kwashiorkor is not the presence of fat, but its *amount*. In other words, it is wrong to think simply of a fatty liver, and leave it at that. A liver with 30–40% of fat is not, as far as I know, found in pneumonia, enteritis or starvation. You may get 10 or 15% in those conditions.

Dean: So you might even distinguish between marasmus and kwashiorkor, severe cases of both, by the measurement of the amount of fat in the liver?

Waterlow: It might be a point of distinction.

Bras: In kwashiorkor, as well as in marasmus, you may get cases with only a small amount of fat in the liver, Dr Dean. When I said that *on the whole* marasmus showed less fat than kwashiorkor I gave averages.

DEAN: Yes. When you say that it shows less fat, do you mean that the slides show less fat? I remember clearly that Dr Waterlow pointed out a long time ago, that to look at a slide gave you really a very poor idea of the actual amount of fat that you could demonstrate chemically.*

BRAS: That is why I started out by saying 'on the whole'. We correspond very well when we compare the histological judgement with fat assessed biochemically, except that, in small amounts the histologist tends to overestimate the fat, and in large amounts to underestimate it.

GYORGY: The middle range is the critical one in marasmus as opposed to kwashiorkor.

BRAS: That is a very good point, I think.

DEAN: We know that the fat can disappear very rapidly under the influence of correct treatment. Are you sure that what you are showing us is not influenced by that possibility?

BRAS: The slides which I showed are definitely influenced by treatment, because the child is not biopsied the moment it comes in. It goes through a regimen of prothrombin-time estimations and so on before it is biopsied. I don't know what the average time is, but usually it is a few days.

WATERLOW: Two or 3 days at least.

GYORGY: Therefore acute kwashiorkor could have already improved during the first 2 days.

BRAS: Yes, especially the child who reacts well to treatment, and who is certainly influenced within a matter of 48 hours.

FREMONT-SMITH: Are all the biopsies taken at 2 days or are some taken at 18 hours? You might have an occasional early case, which might give a clue.

WATERLOW: Never as early as 18 hours, Dr Fremont-Smith. But we usually keep these cases on a low protein intake until the investigations have been done. Our experience is that if they are put on quarter-strength milk, that more or less maintains the *status quo*, and neither allows much improvement nor produces much deterioration.

GYORGY: How do you know that?

WATERLOW: From clinical experience.

CLEMENTS: Of course, part of the answer to all this would be provided by post-mortem examination of the child who comes in at a very acute stage and dies. Have you any such material?

BRAS: We have post-mortem material of children who died within a few hours after admission. At one time, I had the impression that they either die within 48 hours or stay alive. I have done ten post-mortems on the kwashiorkor cases reported in this group, most of whom died within

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* The point I originally made is correctly stated by Dr Bras.—J. Waterlow.

48 hours. They all had a maximal amount of fatty change; hardly any liver cell was excluded.

RAO: What is the distribution of fat in your biopsy specimens? Is it portal or around the central veins? What is the effect of treatment? Where does the fat disappear first?

BRAS: It is predominantly periportal. In all three groups—kwashiorkor, marasmic kwashiorkor, and marasmus, there is a predilection for the outer parts of the lobule.

RAO: The reason why I asked you that question is that in the experimental animal, the fat deposition is central. Can you explain why there should be a difference there?

DEAN: Is it possible that these cases are influenced by the presence of an infection which, alone and without the presence of kwashiorkor, might result in a deposition of fat in the liver?

BRAS: As you, I believe, remarked yesterday, Dr Davies has stated that there is a difference in the distribution of fat in the child with kwashiorkor and the child who dies of an infection. Have I interpreted this correctly?

DEAN: Yes.

BRAS: I agree with Dr Davies in that respect. It is not possible to make a differentiation once the fatty change is maximal, that is, when every cell is entirely filled with fat. But if you take a child who died of an acute disease with fatty change in the liver, I believe that, more commonly than not, the fatty change tends to produce fine vacuoles rather than large vacuoles, and that the fat tends to be more diffusely spread, in contrast with the predilection for the periphery shown in kwashiorkor.

DEAN: Was infection present in your cases?

STUART: Infection is rare in our material. We examined thirty-five of our cases of kwashiorkor, and in only seven of them was there any infection. In five of these there was an infection with *Salmonella typhimurium*.

DEAN: Have you been able to correlate the presence of an infection with any particular appearance in the histology?

STUART: No.

CLEMENTS: How about helminth infestation?

STUART: Helminth infestation in Jamaica is relatively rare, and when they do have a worm load, it is usually very light. It is not an important complicating factor.

BRAS: We routinely check the bowel contents of all post-mortem cases for the presence of worms, because I have a special interest in worms. If I compare my yield here with what I used to get in Indonesia, there is a vast difference; in fact I have not seen one good case of ankylostomiasis yet. What I get is a few ascaris or trichuris or nothing at all, surprisingly.

SCRIMSHAW: People do go astray on this point, and it is probably well to emphasize the way these liver changes can occur from a variety of other causes. Howard & Meriwether (30) in Panama, 2 years ago, observed fatty livers in children who had died within 24–48 hours after admission. They wished to publish their findings under the title of *Malignant Malnutrition*, and thought they were studying a form of kwashiorkor. Careful examination of their cases showed that broncho-pneumonia, nephritis and various other conditions were included in the series. They described a reasonably common pathological picture with a diverse set of causes. The paper was finally published under the title 'Fat disease of liver in infants on the isthmus of Panama'.

BRAS: You will remember that I made the remark that when the liver cell change is maximal, I do not see how you can differentiate between the two causes of fatty infiltration.

SCRIMSHAW: Precisely, but the point is worth emphasizing, for other people may start studies like the one just mentioned, selecting their cases on the basis of a pathological feature of multiple aetiology. These cases were chosen because they had marked fatty metamorphosis of the liver on autopsy; 78% of them died before arrival or within the first 24 hours. The fatty liver, and the relatively sudden death after hospitalization were the factors that linked these cases together.

FREMONT-SMITH: And then they turned out to have pneumonia, nephritis and other things?

SCRIMSHAW: Yes, most of them did.

FREMONT-SMITH: There seems to be a contradiction here. In an earlier statement, I think, Dr Waterlow said it was not supposed that death from intercurrent infection would produce such extreme fatty changes as we had here, and therefore he and his colleague were ruling out intercurrent infection as playing a predominant role. Are not these two statements contradictory?

WATERLOW: I can only give my opinion—

FREMONT-SMITH: No, no! Are the statements contradictory?

WATERLOW: I don't think they are, because I think it is perfectly possible that in the cases of Howard & Meriwether mentioned by Dr Scrimshaw, we have both kwashiorkor and infection. Of course, I don't know the details.

CLEMENTS: Moreover, Dr Scrimshaw has not elaborated on what he means by 'fatty change', in terms of the descriptions we have had this morning.

WATERLOW: There is also the point that if a child has kwashiorkor and a fatty liver and gets broncho-pneumonia, it will die very easily and very rapidly, and that is the kind of case that will come into the post-mortem series.

Fremont-Smith: So these might have been cases of kwashiorkor, after all, in spite of the fact that they had terminal broncho-pneumonia. That is the point I was really trying to make.

Scrimshaw: Some of them might have been, but from the scanty clinical descriptions available, most of them certainly would not meet our criteria for kwashiorkor.

Autret: The notes and photographs of these cases in Panama were shown by Dr Behar to Professor J. Stokes and Professor Gyorgy. Both were of the opinion that most of the cases had nothing to do with malignant malnutrition.

Peña Chavarria: I would like to say that the general description by Dr Bras of the Jamaican cases is just like the ones that we see in Costa Rica. In our first paper, in 1937 (40), we had a description of the liver changes, and I will translate it literally, not as a historical remark but to show the similarity with your description. We say: 'Histologically, an almost total fatty change of the hepatic lobules was observed, more marked peripherally. In the periportal tissue is found a round cell infiltration, which varies in degree from case to case. In some cases, we observed biliary stasis in the bile canaliculi in the central regions of the lobules.'

Bras: I feel that many members of the audience think that not enough attention has been devoted to kwashiorkor, and I am sorry if that has been the case. My original intention was to deal with the liver in the first half of this day and to devote the other half to the other organs. However, there are still a few more problems to present regarding kwashiorkor.

One of the things that has intrigued us, as well as many other people, is the mode of death in kwashiorkor. When our children come to autopsy, in many cases we see a broncho-pneumonia or a middle-ear infection, which satisfies us as being the immediate cause of death. But there are also many other instances in which the immediate cause of death remains obscure. In a personal communication to Dr Waterlow, Dr Abbali, in Cuba (41), has mentioned that he sees a hypoglycaemia with depletion of the liver of glycogen, and he thinks that some of his cases die of hypoglycaemia. Adrenalin in these cases does not give a rise in blood sugar. In a recent article in the *British Medical Journal* by Trowell, Davies & Dean (42) mention was made of the same problem, of the fact that the mode of death was in so many cases unexplained. I wonder whether it would be profitable to discuss this problem, and whether Dr Dean, for instance, would like to give some of his ideas about this very important point in the pathology of kwashiorkor.

DEAN: It is a point which has troubled us a great deal. Death doesn't seem to occur so regularly now as it did, so we have had few opportunities of investigating it.

It sometimes happens that a child who is well on the way to recovery and, as far as we can see, is almost ready for discharge, quite suddenly dies.

STUART: In our experience the child is not one whom you think is ready for discharge, but rather one who has been progressing satisfactorily, and then suddenly seems to deteriorate.

DEAN: Yes. I would go even further than that and say that these are children whom we thought were well, whom we did not expect to die, and who showed no deterioration at all. That is the extraordinary thing. You have not seen that?

STUART: No.

DEAN: Ours have all died overnight or when we were not present, and, as far as we can tell, for no reason whatever. That is what made us think of the possibility of hypoglycaemia. In a review of the literature which I have recently had to do, I found that the same mode of death has been described even from the time when Czerny & Keller (43) issued the second edition of their book in 1928. In their series they had a child who suddenly died, and the same phenomenon has been reported from all over the world. Unfortunately, I have no information at all on why this happens.

BRAS: Do you know what the glycogen content of the liver is in these cases?

DEAN: No.

WATERLOW: Do they have hypoglycaemia?

DEAN: I don't know.

FREMONT-SMITH: May I ask whether these children, if they need an operation for any purpose, such as an emergency appendectomy or mastoid, have any tendency to go into shock? Do they take anaethesia badly? Do we have any clinical evidence about this?

DEAN: I have never heard that there was any tendency to operative shock in our population of children.

WILLIAMS: I should say that my cases certainly stood operation badly. Many cases of malnutrition are very bad subjects, particularly in beri-beri countries. You get all sorts of unexpected deaths. People who have had a period of reduced diet or starvation may apparently recover and then fall down dead or die in their sleep.

FREMONT-SMITH: I raised the question because of the possible analogy to Dr Gyorgy's rats with nutritional cirrhosis of the liver, which were already, according to Shorr's studies (44) practically on the edge of traumatic shock, in the sense that they had no capacity to maintain their blood pressure after slight haemorrhage; they would go right into shock. It seems possible that these children, or some of them, particularly those who have not had treatment, might be in the same situation. This would be an alternative explanation to hypoglycaemia for sudden death, so that either an infection or an operation or an injury would be something they might not be able to stand.

Peña Chavarria: My impression is just the same. As a rule these cases stand secondary infections very badly. Our principal cause of death has been broncho-pneumonia.

Clements: Following operation?

Peña Chavarria: No, as a whole.

Williams: I think that they do very badly under any sort of stress.

Van der Sar: The few cases who died in our experience had the typical picture which Dr Williams mentioned yesterday—cold hands and cold feet. I think it is a picture of what we call 'adaptation syndrome', and therefore in addition to dietary treatment I gave the children deoxycorticosterone, and then many of them improved.

Sénécal: I think that the cause of death in many cases is a secondary effect following the infection which itself often starts off the malnutrition.

Gopalan: In the material which I have, I believe I could recognize three causes of death. There are those cases which develop broncho-pneumonia and die slowly. There are others which die quite suddenly, the type of death to which Dr Dean referred. Then there are a few cases which die after convulsions. If hypoglycaemia were responsible I would not have expected sudden death, but rather convulsions. In the few cases which died of convulsions we tried to push in glucose, but I don't think it worked. My own feeling is that these cases of sudden death may be manifestations of the Friedrichs-Waterhouse syndrome, due to haemorrhage into the adrenals, although I do not have any definite pathological evidence to support that.

Bras: This is not described anywhere to my knowledge, nor have we found it in our series of kwashiorkor. I wonder if anybody present knows of such a case?

Peña Chavarria: In one of our cases of sudden death when the child was improving and unexpectedly died, we found haemorrhages in the adrenals.

Sénécal: We have always examined the suprarenals carefully in cases which died suddenly and have not found haemorrhage, but have found some changes in the zona fasciculata, suggesting a disturbance of carbohydrate metabolism, and also some alterations in the islet tissue of the pancreas. I therefore feel that it is necessary to pay a good deal of attention to the question of carbohydrate metabolism in these cases.

Cruickshank: I should like to implement what Dr Williams has said about adult protein malnutrition. In a prisoner-of-war camp we saw a large number of cases of sudden death, and the mode of death was undoubtedly cardiac irregularity. It may be ventricular fibrillation. We saw cases which had Stokes-Adams attacks with cardiac arrest lasting a minute or two. Some of them recovered; some of them would die several hours later, having had an arrest for 20 minutes in some cases, and then the heart started again. There is no doubt, therefore, that the sudden death in these cases was due to cardiac arrest. But what the mechanism of cardiac arrest was—whether it was an ionic shift—I cannot say. These people, again, were often people who were making satisfactory progress, who were not by any means the most malnourished people in the camp—in fact, the type of case, if you had them in hospital, that you weren't particularly worried about. They often died at night.

Gyorgy: Did they not have beri-beri or any complication connected with beri-beri?

Cruickshank: No, nor did they respond in any way to large doses of thiamine.

Bras: These cases you speak of remind me very much of my own experience, and also of what I read afterwards in the Danish report (6), of how people would die very unexpectedly, after having been walking about. It would seem from the evidence that is given there that these people were in a hypoglycaemic state. Figures for the blood sugar were mentioned as low as 6 mg. %, which is so low that at first one would think it must be a printing error, but it appears again in another part of the book.

Cruickshank: I certainly can't say anything about blood sugars in these people, but I am not aware that hypoglycaemia does produce sudden cardiac arrest or gross cardiac irregularities. I should like some information on that point from somebody else.

Stuart: The cases that we have seen in the wards progress apparently normally, and then suddenly deteriorate and unexpectedly die. We thought in the first place that it might have been due to potassium insufficiency. We have been giving potassium lately, but our results do not yet give any clear information on this point. No electro-cardiographic changes have been found. As regards hypoglycaemia, we have been aware of this possibility, and there have been at least two cases where we have had blood taken within an hour of death. The blood sugar was low, of the order of 60 or 70 mg. %; but it was not low enough to be regarded as the cause of death.

Bras: I wonder whether it is a practical suggestion that blood sugar estimations should be carried out on these patients whenever possible.

GYORGY: I should like to add that not only blood sugar should be measured, but that glucose tolerances should also be done.

WATERLOW: May I recall the original work of Trowell & Holmes (41) which showed that there seems to be some depletion of liver glycogen in these cases. It was a fine piece of work which I think is relevant at this point.

DEAN: There was only one child in that series, and he showed a somewhat impaired ability to store glycogen when glucose was given intravenously. We think the experiment must be repeated.

STUART: We have done liver glycogens here in at least four cases.

DEAN: After giving glucose intravenously?

STUART: No, on biopsy specimens taken after fasting overnight; the figures have been normal as far as we know. The glycogen was usually about 5% of the fresh weight.

GYORGY: That would be rather high, if it is a very fatty liver.

STUART: It is certainly not very low.

WATERLOW: The glycogen content does seem to be high in the human liver.

SANTOS: In the Brazilian literature there is mention of sudden death in cases of malnutrition, and Dr Magalhaes Carvalho has been looking for a treatment to prevent this. He found that a substance known as lipocaic, which is extracted from the pancreas, is beneficial. He reported twenty-nine cases treated in this way with lipocaic and dried skim milk (40), in which they had only three deaths, two from broncho-pneumonia and another one in which the cause of death was not diagnosed. He thinks that this treatment very greatly diminished the total number of sudden deaths.

GYORGY: Practically nobody believes any more in the existence of lipocaic.

SANTOS: Well, at least it is a pancreatic extract, and perhaps that is the reason for its good effects.

HILL: I think it should also be mentioned that the Gillman brothers in their book on pellagra (5) have gone into this fairly carefully, and I think their work should be repeated. Their results are rather equivocal, but some of their cases have low fasting blood sugars, are very hypersensitive to insulin and show no reaction to adrenalin.

STUART: Their conclusions were based, if I remember correctly, on insulin-sensitivity tests done by the subcutaneous route. We use the intravenous route, which I think will tell you much more than the subcutaneous one.

HILL: They used only ten units of insulin and the blood sugars went right down. This dose produced coma in some cases, they were so hypersensitive to it.

DEAN: If you are doing a glucose tolerance test, as I think Dr Gyorgy suggested, it might be combined, if possible, with other tests in which a duodenal tube is used. We know nothing about absorption from the stomach and gut of these children, and if we got the glucose into the duodenum, we would at least know where it was and where we started.

HILL: There is one other thing I should like to add. You remember Le Count & Singer (47) reported sudden death in people with pneumonia who had fatty livers? They attributed it to the fact that the liver could not store glycogen. I think that has been exploded from many sources; for example by Kaplan & Chaikoff (48). In our cases of vomiting sickness, we find, after treatment, that the liver is fatty and yet there is deposition of glycogen; so the presence of fat does not mean that there is no glycogen.

BRAS: The next problem that I want to raise as a pathologist, is the sequelae of kwashiorkor. We know that as fat disappears from the liver, we frequently see a cellular increase in the sinusoids and also in the portal tracts. I have also mentioned that there might be an increase in reticulin in the periportal area, and that leads me to a very important point: what is the outcome of kwashiorkor?

I might refer to the work of Dr Davies, published in the Macy transactions of 1950 (37), where he mentions that he has seen all stages between kwashiorkor and true Laennec's cirrhosis (meaning a portal cirrhosis). I have gained the impression from a study of the literature that about 4 or 5 years ago it was more or less accepted that kwashiorkor led to cirrhosis, and this view was strongly supported, of course, by the experimental dietary cirrhosis which was seen to occur in previously fatty livers.

Personally I think that this view, as expressed in those words, is no longer tenable. Brock & Autret (33) say in their report that areas with kwashiorkor in early life and cirrhosis in later life overlap geographically, but do not completely coincide. They accept the aetiological evidence of both being due to a dietary deficiency, particularly of protein.

In most areas in Africa it has been found that fatty change precedes or runs *pari passu* with fibrosis. But if I may quote Brock & Autret again, they refer to a tribe in East Africa who are meat-eaters, and whose children do not have kwashiorkor, although cirrhosis is very prevalent among the adults of this particular tribe.

I might also refer to the work of Walters & Waterlow (13) in the Gambia, who, as I mentioned before, saw cirrhosis not preceded by severe fatty change. Then the Gillmans, in South Africa, have repeatedly stressed that in their material the fatty change and fibrosis do not run parallel. Finally I should mention the work of Dible (49), who says that fatty change is not a precursor of cirrhosis. In other words, there are many conflicting statements, and I would just like to bring this question into the discussion on the sequelae of kwashiorkor.

I myself am of the opinion that there is at present no conclusive evidence to show that kwashiorkor in itself leads to cirrhosis later in life, and that we must pay more attention to suggestions made by some investigators that the end stage (i.e. cirrhosis) may be a final outcome of two factors, 'A' plus 'B'. In the Gambia Walters & Waterlow postulated malnutrition as 'A' and malaria as 'B'. We saw that in veno-occlusive disease a toxin or some such noxious substance could be postulated as factor 'B' in addition to undernutrition. We have heard that Dr Rao, too, has incriminated toxins. We know that in experimental animals a similar combination has been demonstrated on many occasions. Again, there is the possible role of virus hepatitis. I feel that some exchange of opinions on the role of these factors, and on the sequelae of kwashiorkor might be profitable.

Peña Chavarria: We have seen cases in Costa Rica of cirrhosis in children, and we have discussed the possibility of a nutritional cause or of a virus infection; I would like to know from Dr Bras if it is common here in Jamaica to see children with cirrhosis of the liver from infectious virus hepatitis?

Bras: I could answer the question, if you could change it a little bit. If you ask: do I see evidence of a hepatitis in the kwashiorkor livers? Then the answer is no.

Gyorgy: I might add, however, that according to the most recent pathological studies in the United States, it is generally considered that the fatty liver will often not show marked changes due to viral hepatitis. Studies of blood donors who transmitted the virus to their recipients have been made, and when their livers were examined there was a maximal fatty liver or cirrhosis but no sign of cellular infiltration. The general impression is that such a liver does not respond to the virus in the same way as a normal liver.

Bras: Would you consider that those patients were suffering from viral hepatitis?

Gyorgy: They show more the picture of Laennec's cirrhosis than of viral hepatitis.

Bras: Did they have clinical signs of the disease at all?

Gyorgy: No. We had a very interesting patient who was a chronic alcoholic, and who transmitted hepatitis to recipients about six times within a period of 4 years.

Sénécal: In West Africa we see a great deal of kwashiorkor and a great deal of cirrhosis, but have not been able to trace any continuous connexion between the two. In sixty-four cases of kwashiorkor there was an increase in reticulin in forty-six; in thirty of these the increase was slight and was considered to be normal for the African liver; in twelve it was moderately increased; three were classified as pre-cirrhotic, and one was definitely cirrhotic.

Bras: In children?

Sénécal: Yes. The three cases of pre-cirrhosis were 16 months to 2½ years old, and two of them were malarial. The case of true cirrhosis was 23 months old and did not have malaria. We have been rather struck by the small number of cases with cirrhosis, and have been attempting to explain why there should be so few. One possibility is that the cases of kwashiorkor are so bad that they die before they can develop cirrhosis. The second alternative is that the cases are so mild that they are not diagnosed as kwashiorkor. This hypothesis, that some cases are so mild that they are not diagnosed, suggests that it is necessary to have a test by which one can diagnose mild kwashiorkor.

Fremont-Smith: And see whether it evolves into cirrhosis.

Sénécal: Alternatively, there is no relation at all between malnutrition and fibrosis, the fibrosis being due to infection or other causes. As to these three alternative hypotheses, I have no personal opinion, but I have been struck by the results of work on the newborn. I have done 300 biopsies on newborn infants, particularly in relation to congenital syphilis. Many of these children did not have syphilis, but I have been struck by the fact that in so many livers of African newborn children there was an increase in collagen compared with European controls.

Waterlow: In the Gambia we attempted to do much the same thing. In fact, my colleague there, Col. Walters, did the first biopsy on a child in Dakar, some 6 years ago. Since then Dr Sénécal and his group have amassed this very large amount of material. Walters and I were trying to find the progression from fat to cirrhosis, or rather, from the malnourished infant to the cirrhotic child. We were able to find, as we thought, a continuous development, but not starting from fat (13). In surveying the literature we have not been able to find any conclusive evidence in man of this continuous progression, beginning with fat, that you do find in the rat. This conclusion agrees with that of Dible (40), but has been reached by a different path. Dible's view is that fat has nothing to do with fibrosis, because only in one case in his series of fibrotic livers was there more than 30% of fat. But, experimentally, if you are going to produce cirrhosis or fibrosis in a fatty liver, you have to reach a critical level of fat and keep it up for a certain length of time. I think that Dr Gyorgy would agree with that.

Gyorgy: No, I would not: I'm sorry. This brings me to a chapter which is very close to my heart, indicating my split personality. As a clinician

I am very much interested in your clinical observations. I am doing the same. But I am not greatly satisfied with them, because they are not very well controlled. They cannot be very well controlled, either with regard to the history or to the number. There the experimental nutritionist comes in. I know that Dr Rao and I see completely eye to eye on this problem, and I strongly recommend that you accept at least the facts which I shall report to you in connexion with the problem now under discussion.

In rats you can produce kwashiorkor. The best diet is not a ration too low in protein, but one which does not contain large amounts of animal protein. The best diet, containing peanut meal and only a very small amount of casein, has been recommended by the group working in the Polytechnic School of Alabama. On such a diet the animals will show a fatty liver, generalized oedema and hypoproteinaemia. The syndrome can be prevented by lipotropic substances such as choline and its precursors (50).

However, I personally do not believe and never have believed that fatty infiltration as such is an essential prerequisite for cirrhosis. In the Macy conferences we have repeatedly had rather heated arguments with my very good friends Sir Harold Himsworth and Dr Best, who still believe that fatty infiltration is a prerequisite for cirrhosis. It is not. I never believed it and I still don't believe it. You may get cirrhosis without too much fatty infiltration, and very often the fat disappears, as Hartroft has shown beautifully, when there is not much cirrhosis. The most convincing findings, which are very pertinent to the kwashiorkor problem, have been presented by Dr Popper in studies on ethionine-produced cirrhosis (51). Ethionine is the metabolic antagonist and homologue of methionine. Instead of methyl-, it is an ethyl-amino acid. Ethionine will produce very severe fatty liver, but this very severe fatty liver is of a temporary nature. It disappears completely, and when it disappears there is at first no cirrhosis.

FREMONT-SMITH: It disappears while you continue the ethionine?

GYORGY: Yes. After the fatty infiltration disappears the cells look normal. Then fibrosis starts, and you have a fairly typical, I won't say severe cirrhosis, but still one which would cover your criteria for cirrhosis.

Therefore, you have here, in the ethionine-produced nutritional cirrhosis—I will come back to this adjective, 'nutritional'—the same history of liver injury as we see in kwashiorkor in countries such as Uganda. There you have quite a number of fatty livers in young infants and no cirrhosis. Then, suddenly, between the ages of 6 or 7 years and 18 years, there appears a very large incidence of typical cirrhosis. If you telescope this time period into the shorter life span of the rat, you will see the same results occur in the rat in the same sequence.

I said 'nutritional'. Somebody could say ethionine is a toxin, and it still could be possible that it has some toxic effect; but the fact remains that when you compensate for the ethionine with the proper amount of methionine, you will prevent all the lesions, because there develops a typical metabolic competition between the amino acids.

Here we have a beautiful, rather singular experimental set-up, which obviously does not compare in every respect with the clinical set-up in parts of the world where there is this apparent discrepancy—first a fatty liver, then no fatty liver and then cirrhosis. But still, we have here an experimental parallel to it, and I think it is an impressive parallel, because with high protein, or in this case a protein which contains a lot of methionine, cirrhosis is completely prevented.

SCRIMSHAW: True, but can't we object to your use of the term when you say you find kwashiorkor in rats? Isn't kwashiorkor a clinical syndrome, defined as a disease in infants? Your findings are similar to it, but you are not finding kwashiorkor.

GYORGY: But then you would throw out of the window any experimental nutritional work.

SCRIMSHAW: Not at all. I am just objecting to the use of the term.

GYORGY: Thirty years ago I was just as rash and young as you, and when Hess and Steenbock claimed that they had produced rickets in rats, I said: 'That is not rickets in rats: the histologist can demonstrate very important differences between this rickets in rats and in infants. Secondly, they had to use a pathological calcium phosphorus ratio to produce it. That is not rickets.' When the fact came out that the same substance cures the rickets in the infant and in the rat, then I learnt my lesson. The lesson is that experimental nutrition is the real basis for any nutritional work.*

FREMONT-SMITH: Would you accept this correction: that instead of saying you had produced kwashiorkor in rats, you had produced a condition in rats which resembles kwashiorkor and which has the following characteristics?

GYORGY: Yes. I don't want to be too pedantic when it comes to terminology, and I accept that. Personally, I don't see any difficulty in relating the high incidence of fatty liver in young infants, and cirrhosis and hepatoma in young adults, to protein malnutrition, and I would venture the prophecy that by improving protein nutrition you will not only eliminate kwashiorkor but you will also eliminate cirrhosis and hepatoma.

BRAS: I think it might be profitable if we go a little further into the aetiology of liver cirrhosis, as it is accepted nowadays, leaving aside for the moment the sequelae of kwashiorkor. I think there is much to be said for a double aetiology, and I would like to hear the feeling of others on this. I might quote Bergeret (52), who says that if the adult American or European does not have cirrhosis of the liver, it is because, on leaving his mother's breast, he was supplied with the necessary nutriments, which makes him able to face life like a happy bridge player, with as many trumps in his hand as possible.

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* One can cite many cases where the final outcome has not been so fortunate. For example, many investigators have reported eclampsia in animals, although such claims have never been given general acceptance. The book of the Gillmans suggests that pellagra is not as simple a disease in humans as the condition produced by niacin deficiency in experimental animals.—Scrimshaw.

I believe that I am not far from wrong when I say that, leaving aside biliary cirrhosis, there are at present three aetiological factors very seriously under consideration for producing cirrhosis. The first is the action of so-called liver poisons. The second is deficiency in specific nutriments, either directly or indirectly, as Professor Gyorgy has just pointed out. The third is a previous attack of virus hepatitis. The three factors are, of course, closely interdependent and this accounts for the difficulty in unravelling the precise importance of each and for the different opinions that are held about the relative importance of each.

As you know, there has been and there still is much talk about alcohol. As far as that is concerned, I have been much impressed by the experiments of Professor Best (53) and his group who proved that in rats if you substitute alcohol for an equicaloric amount of sugar, you get the same effect—a fatty change—which, in both conditions, can be prevented by a little choline.

That deficiency of specific food factors in the absence of known liver poisons can itself lead to hepatic necrosis and cirrhosis is an idea based particularly on the experimental work of Gyorgy & Goldblatt (55), Daft, Sebrell & Lillie (56) and Himsworth & Glynn (57) and on clinical studies of Trowell, Waterlow, the Gillmans and others.

Many investigators have brought forward evidence that infective hepatitis may result in cirrhosis. There is a striking difference in the severity of the disease in various parts of the world, and although this may be due to variations in the virulence of the causative virus, nutrition also seems to have an important influence. In an outbreak of serum jaundice among American troops the mortality was 0·2 % as compared with 2·4 % among Brazilians. An even more convincing example of the naturally occurring disease was reported in Africa by Findlay (58). Professor Fernando and his colleagues (59) have given a further indication of the influence of nutrition on the course of infective hepatitis and on the type of cirrhosis that may ensue. The mortality among the cases of hepatitis studied by them was 18·5 %—almost 100 times that in civilian epidemics in Europe or the United States.

I may also refer to the work of Straub (60) in Indonesia, who did autopsies on sixty cachectic Indonesians dying of starvation, and compared their livers with those of well-fed Indonesian soldiers who had died an accidental death. On the basis of that investigation he postulates very strongly that the cirrhotic changes which he saw in his cachectic Indonesians were the result of a virus hepatitis, which had produced a different effect in the two groups; that is, the virus had a chance to reach both groups, but in the one it produced after-effects in the form of cirrhosis, whereas in the other group it did not.

In a preliminary communication which I have recently had from workers in Indonesia it is stated that at present cirrhosis is more and more often seen combined with inflammatory changes, as reported by Straub. The condition is also becoming more prevalent among younger people, and even among infants and children. General conditions in Indonesia now, and especially the general level of nutrition, are very different from those that obtained before the war.

I would like to close this discussion on the liver by inviting your views on the role of kwashiorkor in the aetiology of cirrhosis. My own opinion is that it is not proven that kwashiorkor, as such, gives rise to cirrhosis; I think that probably, in addition to conditioning by protein malnutrition, there is needed a second factor, which may be very different in various parts of the world. This would account for the apparent incongruity in different places. This second factor may be alcohol, it may be a toxin, it may be virus hepatitis, it may be many more things of which we are not aware.

Sénécal: I was very much impressed by the sections I saw some 3 months ago in Dr Gyorgy's laboratory of the livers of rats put on a regime deficient in methionine. The fatty infiltration, however, was centrolobular, whereas in the human cases it is always peripheral. The ordinary nutritional fatty liver in the rat is centrolobular, and the ethionine fatty liver is peripheral, as in the human being; this leads me to ask Professor Gyorgy whether he would not abandon his hypothesis that the ethionine fatty liver is an effect of nutritional deficiency, and consider it a toxic effect? Moreover, I believe that ethionine has never been found in the human body, and therefore could reasonably be considered to be a toxin. Of course, it does not act directly, but by neutralizing or counteracting the action of methionine.

Gyorgy: I did not deny the possibility that ethionine, in addition to its being an antagonist of methionine, is a toxic factor. I used ethionine only as an example, which illustrates the possibility that you can produce a kwashiorkor-like disease and the whole sequence of liver changes.

However, I would like to comment further, if I may, on the question raised by Professor Sénécal, whether I have abandoned the nutritional aetiology of kwashiorkor and post-kwashiorkor cirrhosis. I have not. Such a thing may happen. Ethionine also produces cancer, according to the latest studies of Dr Popper (59). Now, first of all, I would like to say that you can produce all these changes, including the perilobular fatty infiltration, without ethionine, by purely dietary means. The pathologists usually point out that the fatty infiltration of the liver in the rat fed a diet low in protein is centrolobular, whereas in man, in kwashiorkor and in alcoholic fatty liver, the fatty infiltration is usually periportal. Dr Shils of Columbia University presented some very interesting experiments bearing on this point at the International Physiological Congress in Montreal (60). He took a set of rats and put them on the usual experimental cirrhosis-producing diet. The first change is fatty infiltration, which is centrolobular. These rats were kept on that diet, on which they did grow, but they were not fertile. In order to get a second litter, he gave them vitamin B_{12}, and then they became fertile and had a litter which survived. The mothers were fed B_{12} only before pregnancy, during pregnancy and then during the lactation period. The litter, after weaning, was put back on the original diet, and they developed fatty liver, with *peripheral* fatty infiltration.

Dean: I have an interesting experiment, along similar lines, which I have never published because I wanted to repeat it. We have a local population that feeds on cooked banana, so I fed weanling rats on a diet of nothing but cooked banana. To my pleasure they developed fatty livers. I was repeating this experiment under various conditions, and ran into a period when I could no longer get fatty livers; to cut a long story short, I found that there was a fault in my experimental technique and that I was, in effect, supplying some vitamin B_{12}. I then went back to the source of my rats, which at that time happened to be out of my control, and found that the weanlings came from mothers on a vegetarian diet, in which there was no B_{12}. We were able to go on from that point to the finding that if we supplemented the diet with a little B_{12} or gave a short period on a high protein diet, we could not produce fatty livers in the weanling rats by means of this diet, which otherwise worked in 100% of cases; so it seems that you must always look back to the generation before to see whether there has been any possibility of the weanling rats being protected by B_{12} or perhaps by methionine, or perhaps by animal protein which the mothers receive.

Fremont-Smith: It seems to me that that is a very pertinent observation. We might put it the other way and say that perhaps children get kwashiorkor because the mothers have *not* been protected.

Bras: Is kwashiorkor a congenital disease? A question asked by others before.

Fremont-Smith: That is putting it too sharply, but in the multiple aetiology that you were emphasizing, Dr Bras, the failure of the mother to be protected during pregnancy and nursing might be a factor.

Scrimshaw: That brings up a point which I mentioned at the beginning of this discussion, about the child being apparently all right, but predisposed to nutritional difficulty later on. In a little while we will present some data from Central America showing that the child is not all right; that in this area he is born with a number of handicaps. This point also bears on the interpretation of comparative feeding trials with milk and with soya protein, such as the one carried out by Gomez, in which in 10 months he was unable to determine any difference in effect between the two. The child may have been sufficiently protected during that time, but if the trial had been continued longer, differential effects would have been observed. Undoubtedly, Dr Dean will have more to say on the point later.

Rhodes: If this were so—and perhaps I am drawing the parallel too directly—then surely kwashiorkor would be much more a familial disease than in point of fact it is? The children of the same mother in one family are usually subjected to the same stresses and strains, nutritional or otherwise. But I am not aware, though I may be wrong, that there is any strong familial tendency in kwashiorkor.

Dean: We have considered that point. There is a very interesting corollary to this. I myself have had one case of kwashiorkor in a family of several children, and I could see no reason why the other children should not have it. Therefore what I did was to give my weanling rats a very short period of protection; I found that a day or two on a high protein diet or a day or two on a methionine diet or a small supplement of vitamin B_{12} was sufficient to protect the rat from developing a fatty liver. I think that children in the same family, at a susceptible time, might by some fortunate accident be able to receive some protective substance for just long enough to prevent them from ever developing kwashiorkor. They get stocked up with the necessary protective materials.

Fremont-Smith: Or the mother might be protected in one pregnancy, and not in another. It is a possibility.

Burgess: Dr Oomen in Indonesia recorded the disease in one twin, the other being perfectly healthy (61). On the matter of the cause of cirrhosis, we seem to assume that the dietary conditions to which the child is subjected after an acute attack of kwashiorkor are the same all over the world but in fact they may differ quite a lot. In some countries there is a period after weaning when the disease may occur, but if the child survives this he goes on to a relatively good diet. In other countries, where the staple food is cassava, there may be a chronic deficiency of protein throughout life.

György: I would like to make only one comment on Dr Bras's presentation with regard to the dual aetiology, 'A' and 'B', as he calls it. 'A' would be a nutritional factor and 'B' may be a toxin?

Bras: Yes.

Gyorgy: This morning Dr Bras reported his observations in children with v.o.d. (venous occlusive disease) and, in general these children did not have much fatty infiltration, although they were on a low protein diet. Is that correct?

Bras: Yes, I think that in general is true. There are not many livers from cases of v.o.d. which show much fat.

Gyorgy: I have been asked here in Jamaica how it is possible that some patients fed a low protein diet develop a very fatty liver and nothing else, yet others with similar poor diets low in protein do not develop a fatty liver, or not much fat, but get v.o.d. If you put animals on a low protein diet, you will get a fatty liver. But if you take these animals and add butter yellow—a hepatotoxin—then you do not get much fatty change; you get some, but not much. First you get cirrhosis, and much later, hepatoma. But you do get cirrhosis.

Cruickshank: The evolution of the cirrhosis follows what pattern?

Gyorgy: Cirrhosis starts on this low protein diet in six weeks.

Cruickshank: What is the earliest change in the liver?

Gyorgy: Not much fat, no massive necrosis—scattered necrosis of isolated cells; then, proliferation of the bile ducts and cirrhosis, and then later, after 6 months, hepatoma. If you put the same rats on a diet high in protein but with the same amount of butter yellow, you don't get anything; you don't get necrosis of the liver cells, you don't get cirrhosis, and you don't get cancer.

Again, I recently obtained some senecio extract through the courtesy of the workers at the University College of the West Indies and chiefly through Professor Asprey, Professor of Botany. Senecio extract, in acute intoxication, produces the changes of v.o.d. These changes were described in the literature by Seltzer and his colleagues (26), and I am very glad we have already drawn attention to this in the report of the Gambia Conference ([illegible]). But if you conduct a more or less chronic experiment and control rats are fed a diet which produces fatty liver, then, as I understand from the histological reports obtained from my collaborator, Dr Goldblatt, the rats fed senecio extract show either no fatty infiltration or much less than the control rats without senecio extract, but they show very pronounced toxic changes.

Bras: In the cases of v.o.d. we have had we find fatty changes when the patients belong in the kwashiorkor age group, while in the higher age groups (in which there is less kwashiorkor) we also see less fat. So I am inclined to think that the age factor has a very important influence on the amount of fat. But, of course, I do not touch on the point which Dr Gyorgy made; is there less fat than there would have been without v.o.d.?

Gyorgy: I may say that added protein will prevent everything in the senecio-treated rat as well as in the control rat.

Hill: The rat is a peculiar experimental animal, and you, Professor Gyorgy, know well the effects of temperature on damage to the liver. I wonder if anyone is familiar with kwashiorkor at high altitudes in the tropics?

Scrimshaw: Our most studied centres of incidence of kwashiorkor in Guatemala are at about 6000 or 6500 feet. If Dr Alberto Hurtado of the High Altitudes Institute (Institute Biologico Andino) in Peru is correct, this altitude is not sufficient to produce physiological changes.*

Gyorgy: The most revealing experiments on dietary livery injury in rats in relation to environmental temperature have been presented by Naftalin(63).

Clements: If, Dr Bras, you have finished with the liver, we might now pass on to discuss other organs. Today we are considering pathology—that is, things observed in tissues with the microscope; perhaps we may have time on another day to try to draw all this together—the biochemical, clinical and pathological material. If you agree, then I suggest that we might start with the pancreas.

Bras: I think it is appropriate to devote a little time to the pancreas, because this is an organ which has been reported to be involved in kwashiorkor in many parts of the world; in fact, in recent publications I gather the impression that everybody seems now to be seeing the histopathological changes in the pancreas that were originally reported by Davies(65) in Uganda, by Waterlow(66) in Jamaica, and by Veghelyi(67) in Hungary, and that were suggested by the clinical observations of Carvalho(46).

Here in Jamaica we do see the changes that have been reported by others, such as atrophy of the acini, a decrease in the zymogen granules of the cells of the acini, a widening of the ducts, a preponderance of the epithelium of the ducts because of the relative atrophy of the acini, and—presumably the final stage—fibrosis.

I must say that although the pancreatic changes are seen in our material, we have not been very much impressed with their severity. Recently Dr Clearkin and I(68) have studied autopsy material of forty-nine children under 10 years of age, and have drawn a comparison between cases of kwashiorkor and marasmus and other children who had died from miscellaneous diseases. Table 13 shows that of the sixteen cases of kwashiorkor and marasmus, three had a normal pancreas. In the other thirteen cases the most common finding was a diminution or total lack of zymogen granules (eight cases). Atrophy, fibrosis and preponderance of intercalated duct epithelium were found less often.

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* Kwashiorkor has been recorded in Assam(64) at a similar altitude.—Editor.

Table 13. *Frequency and type of pancreatic lesion observed in forty-nine Jamaican infants and children*

Group	Number	Histopathologic changes in pancreas. Number showing							Age in months			
		Atrophy	Degranulation of acinar cells	Dilatation of ducts	Apparent increase in intercalated ducts	Fibrosis	Retardation in development	Metaplasia	0–6	6–12	12–18	18+
Kwashiorkor	With pancreatic change, 10	3	8	3	3	2	.	.	1	8	.	.
	Without pancreatic change, 1	.	.	.	.	.	.	.	.	.	1	.
Marasmus	With pancreatic change, 3	2	.	.	1	1	.	.	3	.	.	.
	Without pancreatic change, 2	.	.	.	.	.	.	.	.	1	1	.
Miscellaneous, with fatty liver	With pancreatic change, 15	9	5	4	.	.	.	.	7	2	.	6
	Without pancreatic change, 7	.	.	.	.	.	.	.	1	2	.	4
Miscellaneous, without fatty liver	With pancreatic change, 2	.	.	.	.	.	2		1	1	.	.
	Without pancreatic change, 9	.	.	.	.	.	.	.	3	2	1	3

(Table reproduced by courtesy of the editors. *Documenta de Medicina geographica et tropica.*)

The miscellaneous group numbered thirty-three cases, and of these twenty-two had fatty livers; in fifteen of these there were also pancreatic changes. Of the eleven cases that had no fatty change in the liver only two showed any detectable lesions in the pancreas. Statistical evaluation of these figures in the miscellaneous group reveal that there is a high degree of association between fatty change in the liver and pancreatic pathology, which is very unlikely to have occurred by chance.

Therefore approximately 70% of cases in the miscellaneous group which had fatty livers, but did not present clinically as kwashiorkor or marasmus, also exhibited some abnormality of the pancreas; this incidence is about the same as in the kwashiorkor-marasmus group, about 80% of whom showed pancreatic changes. It is obvious on examining the table that except for fibrosis and apparent increase of intercalated ducts there were no outstanding differences in pancreatic pathology between the cases of kwashiorkor and those showing fatty livers in the miscellaneous group.

I am not in a position, of course, to say too much about these figures as yet. I simply give them to you with the following statement, that we do see pancreatic changes in a large number of cases which are not diagnosed clinically as kwashiorkor. As far as we can see, fibrosis is a thing which is relatively rarely seen. I have the impression that the fibrosis, as far as the reports go, is seen more in Uganda than anywhere else. I don't know whether that is because the kwashiorkor there has been present for a long period of time.

To my knowledge, even in experimental animals, where of course conditions are much better controlled than in any clinical case, it has not so far been possible to correlate any structural changes in the pancreas with any specific deficiency.

MACKAY: How do you measure zymogen? What is your histological technique?

BRAS: We see the granules in our haematoxylin-azophloxin slides. I also think that phosphotungstic acid-haematoxylin is a stain which tends to bring out zymogen granules rather well.

MACKAY: This is human material, post-mortem material?

BRAS: Yes.

MACKAY: I myself haven't tried to use post-mortem material but I find very great difficulty, even using fresh animal material and employing special techniques, in getting a really clear picture of the zymogen granules. We use a modified Regaud fixative, with post-chromatization. I have tried almost every possible approach to this, and that is the only way I can demonstrate the zymogen as discrete granules, or the only way to measure the zymogen content (69).

There is another point. You are talking about the amount of zymogen granules present in the pancreas. Pancreatic secretion does adapt itself to diet in a rather interesting way. For instance, if you alter the pattern of the diet, the relative concentration of the enzymes in the pancreatic juice alters. A reduction in the enzymes or the amount of zymogen in your cells may not be the result of a faulty supply, so to speak, of material to the pancreas; it might be simply an adaptive process to a poor diet as a whole.

Bras: In reply to this question of the visibility of zymogen granules, I am afraid that we might be looking at different things. The zymogen granule is a thing which I think the pathologists find no difficulty in seeing; admittedly, they do not go for the finer structural detail. In our sections it is a pinkish material, above the nucleus, towards the lumen. Whether these are the same zymogen granules that you are referring to, I don't know; nor would I be prepared to say precisely what these granules contain.

Mackay: I have seen what you describe very often. The methods I have mentioned and which have been used by other workers who have been studying the physiological aspect, particularly in animal material, show the appearance of these granules as very distinct discrete little globules, extremely numerous. The material I have seen from the usual post-mortem preparations is very different, and I would be hesitant about estimating the zymogen content of a cell in preparations of this kind.

Hill: You once remarked, Dr Bras, that in the healthy corpse—if I may so express it—the pancreas generally undergoes autolysis very quickly, but if there is a deficiency in proteolytic enzymes then the post-mortem change in the diseased pancreas is much less. Did you find that in the kwashiorkor cases?

Bras: When I made that statement, I was referring, in the first place, to the severely starved individuals whom I had seen in Indonesia, the same group on which Dr Straub carried out his investigations (54). It sometimes took a very long time before we could get permission for autopsy, yet it struck us at that time that there were no autolytic changes in the pancreases (which were very small), and then we said to one another, 'Of course, there is no autolytic enzyme there; that is why.'

Dean: Davies has repeatedly made exactly the same observation in Kampala; in fact, I think that was one of the first things that led him to further investigation of the zymogen granules and so to duodenal enzymes. He noticed, in comparable cases with and without kwashiorkor, that the pancreas of the case with kwashiorkor failed to autolyse to anything like the same extent as in the other cases.

The presence of the zymogen granules in the pancreas and in other secreting organs is believed to be associated with the production of enzymes

Have you actually been able to measure the duodenal enzymes in these cases and correlate them with the appearance or lack of appearance of zymogen granules?

BRAS: We have not yet carried out any studies of duodenal enzymes.

DEAN: In Davies's material there is a correlation with the amount of duodenal enzymes, as Thompson & Trowell have shown (72).

SÉNÉCAL: I would like to confirm the communication from Brazzaville last December (70). Twenty-four out of twenty-five cases of children dying of kwashiorkor showed lesions of the pancreas. These lesions are completely comparable to those described by Davies in Kampala. I emphasize this point, because there is a certain amount of argument as to whether or not kwashiorkor exists in Dakar. All these pancreatic lesions are seen in undernourished children. In four cases the lesions were mild and in one the pancreas was normal. In the mild or early lesion the acini are beginning to lose their rounded structure and are heaped together, and there is a very early fibrosis. In the more advanced case the acini have lost their normal structure completely, and the cells of the pancreas have lost their normal aspect. The gland takes on a lymphoid appearance, where islets of unrecognizable cells are lost in bands of fibrous tissue. This atrophy of exocrine glands was found in twenty-two out of twenty-five cases. In two cases, to our surprise, we found the picture of fibrocystic pancreas with dilatation of the ducts and much mucus. One specimen was shown to Dr Andersen in New York and she said that the appearance was completely comparable to that of fibrocystic disease of the pancreas in the U.S.A.

There were certain special clinical features about these two cases. All except three of the cases of kwashiorkor appeared between 16 and 33 months of age; these two infants with fibrocystic pancreas were among the three that were less than 16 months old. One was still being nursed at the breast, and died after only 1 day in hospital. One case, however, was in hospital for a month, and a diagnosis of fibrocystic disease was not made because it presented the classical picture of kwashiorkor.

These pancreatic lesions found in cases of kwashiorkor were also observed in the histological examination of organs from children who, clinically, were not suffering from kwashiorkor. In eighteen cases the histology disclosed changes in the liver and pancreas typical of kwashiorkor, though in children who had died of another disease such as mastoid infection, otitis or pneumonia. This poses the question of how to detect the larval forms of kwashiorkor or, alternatively, whether there is a separate aetiology for the pancreatic lesions in those cases. Dr Camain and I have observed and commented on the hypertrophy of the islands of Langerhans in many of these cases (71).

Bras: Dr Davies, however, specifically denied ever having seen changes which looked anything like fibrocystic disease of the pancreas in kwashiorkor.

Sénécal: I am aware of Dr Davies's view, and therefore I took the precaution of taking these sections to New York and showing them to Dr Dorothy Andersen, to make sure that they were true examples of fibrocystic disease. But they differed a little clinically, in being younger than the usual age at which kwashiorkor presents.

Gyorgy: And they were fed on breast milk.

Clements: Is it possible for a child to have fibrocystic disease of the pancreas and subsequently get kwashiorkor?

Sénécal: Kwashiorkor generally appears after weaning, so it is unusual for the condition to develop so early.

Gyorgy: Why is it not a congenital fibrocystic disease? I think it has nothing to do with kwashiorkor. You will not cure it with protein, since it is not a primary protein deficiency.

Sénécal: It probably is congenital. I don't think it follows from these cases that protein deficiency can lead to the fibrocystic lesion of the pancreas, but rather that the lesion exists, and it is necessary to make a differential diagnosis between it and kwashiorkor. Both these babies died of broncho-pneumonia, but it is impossible to tell whether it was the usual type of broncho-pneumonia, or secondary to the fibrocystic disease.

Fremont-Smith: The only differential diagnosis from kwashiorkor is by autopsy?

Sénécal: Yes.

Waterlow: Would not the change in duodenal enzymes on treatment give you a differential diagnosis?—because according to the findings of Dr Thompson in Uganda (72) in kwashiorkor they come back very quickly on treatment, whereas in fibrocystic disease they do not.

Dean: I think the therapeutic test is the best method of distinguishing the two. As Dr Gyorgy said, the child with fibrocystic disease will not improve on milk, but the child with kwashiorkor will improve on milk and its duodenal enzymes will be restored. I think those are the best diagnostic criteria to distinguish the two conditions.

Fremont-Smith: Do any of those enzymes appear in the urine?

Dean: Amylase does.

Fremont-Smith: I was wondering whether you could get thereby a diagnostic test?

Dean: Amylase in the urine, or amylase in the blood, would do it well, I think. But not all the amylase is produced in the pancreas.

Hill: It would be highly significant in the urine as an index. There is another point: your remarks, Dr Senecal, immediately made me think, did you look at the salivary glands? In our cases of kwashiorkor I looked for changes in the salivary glands and I haven't seen them, although if there is any effect on the pancreas, you would expect it also to affect analogous secretory glands, like those of the salivary system.

Sénécal: We did not examine the salivary glands.

Clements: The Uganda group has reported hypertrophy of the parotid.

Bras: On treatment the parotid swells and becomes hypertrophic. These are similar changes to those reported for the pancreas, going on to cellular infiltration and fibrosis.

Dean: I have Davies's account of it (73). He is talking about the salivary glands, and says 'atrophy is not easily detected by clinical examination in children with kwashiorkor because of the abundant subcutaneous fat and the oedema. Microscopic examination reveals that there is marked atrophy of the parotid gland (the submaxillary gland being less affected) due to shrinking and degranulation of the zymogen secreting cells, the mucus secreting cells being less, if at all, atrophied. There are no changes in the ducts or blood vessels, and in the early stages there is no cellular infiltration, though there may be an increased amount of fat in the parotid glands. Fibrosis seems to start around the atrophied and often dilated acini, and the fibrous tissue may be infiltrated with lymphocytes, especially in older children. Sections of the enlarged parotids show great secretory granular enlargement of the acinar cells which stain very deeply. Mitotic figures are not seen and there does not seem to be any increase in the number of cells present, so that the enlargement would appear to be a true hypertrophy following atrophy.'

Williams: I don't think parotid enlargement is at all specific for kwashiorkor. I first noticed swelling of the parotids when I was in Macedonia in 1926, working with the refugee population. Their basic diet was barley bread and onions and a very little cheese. I wasn't working with hospital patients at all, but in school children the parotid gland was very often swollen. I think Dr Burgess will bear me out that in Malaya after the war enlargement of the parotid was very common. Here in Jamaica we have seen it in cases that do not appear to have any of the symptoms of kwashiorkor, in both adults and children. It is not at all specific.

Cruickshank: In the adult cases we had in Singapore—and they were very common—there was, I think, only a minimal degree of protein malnutrition. There were two phases to the picture; first there was the early stage, when the glands would go up and down regularly throughout the day. My own glands at times would swell up, not with any relation to meals, and go down again in the most remarkable way, without any conscious salivation accompanying the swelling. Then in the later stage, which I didn't see often in Singapore, but which was common in the prisoners in Thailand who were on a much longer period of protein malnutrition, the glands became hard and firm, and a number of them became infected and broke down. There we were certainly not dealing with kwashiorkor, but with adult protein malnutrition, and it was a very common syndrome indeed.

Williams: In the first stage the gland is very soft, but later it becomes fibrous.

Hill: Davies mentions some difference between the maxillary and the parotid. It is surely well known in surgery that the parotid is very prone to infection, which might account for the swelling.

Dean: I had to stop somewhere in this quotation, so I stopped just before Davies went on to explain how parotid gland enlargement had been described by writers in different places, including McCance, Dean & Barrett (74). That was our work in Germany. One particular case was a man who had hunger oedema and died, but not of hunger oedema. I was able to get the parotid and take it back to Cambridge, and there was no suggestion whatever of infection. It was hypertrophy with no other change. So far as I know, Davies has never mentioned the concomitant appearance of infection in any of these parotid glands.

Clements: Are there any further comments on the pancreas? If not, I will ask Dr Gopalan if he would like to say something about the heart.

Bras: May I just introduce the subject briefly by saying that the heart changes described in malnutrition have not been seen by us in Jamaica. There are two sorts of heart changes on record. The first is the one originally termed by Davies 'endomyocardial fibrosis', in which he finds thrombi, mostly in the apex of the heart, especially in the left ventricle; this condition occurs in both males and females between 20 and 40 years of age. In the other condition, as described lately by Gillanders and his colleagues (75) in South Africa, all ages were represented. In contradistinction to Davies's cases, the hearts were enlarged and hypertrophic and originally were found to have fewer thrombi. In a later publication (76) thrombi are also reported.

The patients die of chronic cardiac failure. The authors accept the background of malnutrition. However, they say this must be of long standing. Here we have had only one heart with thrombi attached to the left ventricle, and in that heart the evidence of a nutritional cause was not at all convincing, so we have no experience of that condition.

Dean: As far as I know, Davies makes no connexion between endomyocardial fibrosis and kwashiorkor.

Bras: He calls it a heart in malnutrition.

Dean: Yes, but he does not postulate an association with kwashiorkor.

Gopalan: We have been interested in the question of cardiovascular manifestations of protein malnutrition for some time. I don't think that our observations have reached the stage where we can point to any definite conclusions, but I will just indicate the problems which confront us.

We have carried on electrocardiographic studies in cases of kwashiorkor and in cases of hunger oedema in adults, and we find that at the height of the disease, in both children and adults, there are some striking abnormalities in the electrocardiogram. These abnormalities may be reversed after treatment with a high protein diet, but they are not influenced by treatment with thiamine or with vitamin E. They fall mainly into four categories (Text-fig. 11 A–D).

In the majority of cases, both adults and children, we find bradycardia, which is of the sinus type (A). In practically every case investigated, there is a profound diminution in the amplitude of all deflexions indicating an abnormally low voltage (A–D). Sometimes the *T* waves in the standard limb leads and *V* leads are actually inverted before treatment (B, C). Thirdly, in a few cases, we also find a prolongation of the *QT* interval in relation to the cycle length. Lastly, very occasionally we get abnormalities of rhythm—including nodal rhythm (D); these abnormalities are reversed on high protein diets.

SÉNÉCAL: Is there loss of oedema in the interval?

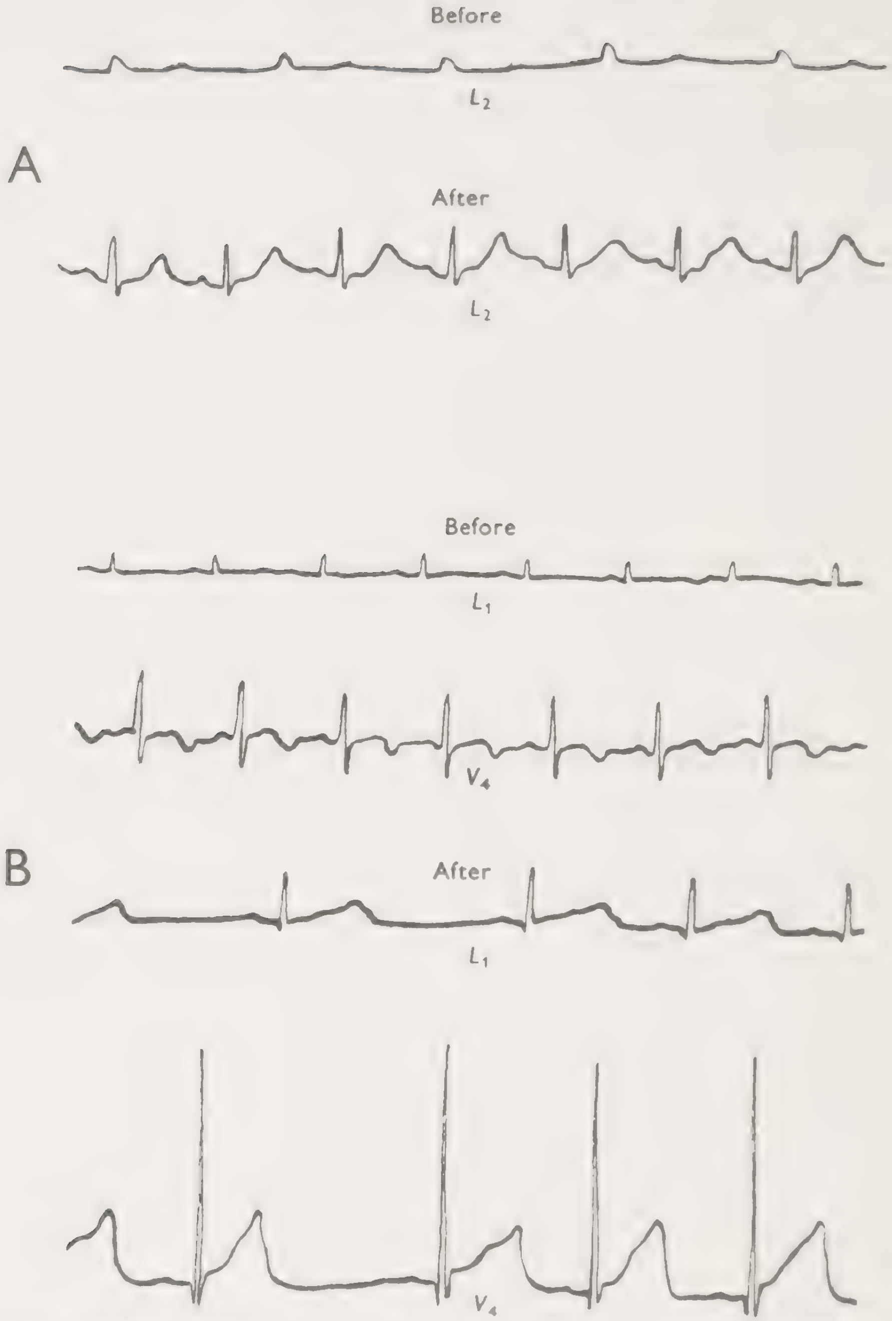
GOPALAN: Are you suggesting that the diminution in the amplitude may be the result of mechanical interference with the electrical conductivity resulting from the oedema? I do not think so, because we have found these same abnormalities in cases of severe malnutrition without oedema.

SÉNÉCAL: One of your electrocardiograms (B) shows evidence of tachycardia.

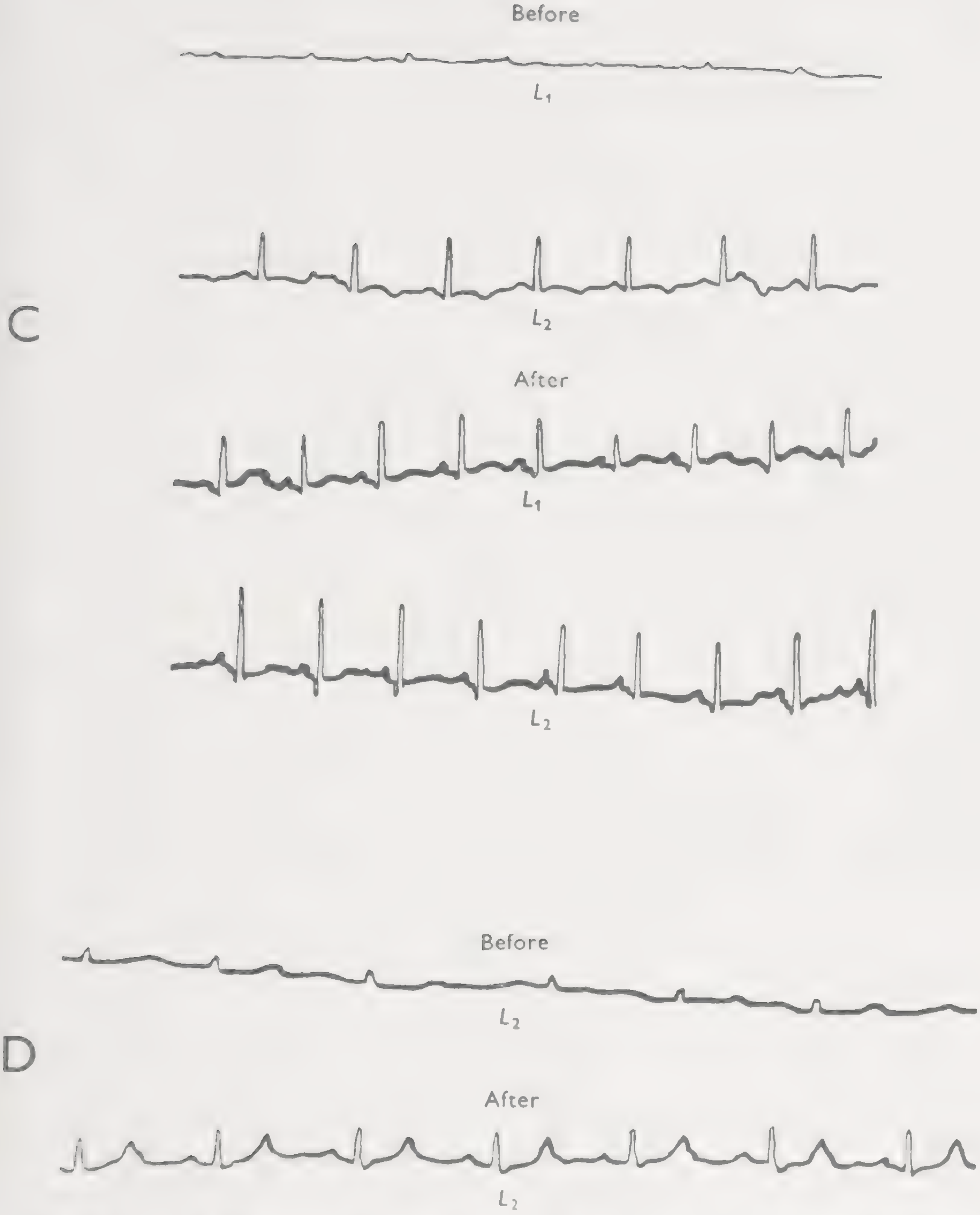
GOPALAN: Usually we get bradycardia, but in some of these children who are excited because of the examination we observe tachycardia.

FREMONT-SMITH: These are older children, aren't they, than the usual type we have been talking about?

GOPALAN: Yes, most of these children are about 4 years old. In adults we also find morbid anatomical changes—cardiac atrophy, Pl. 18 (1), and myocardial fibrosis with increased interstitial tissue, Pl. 18 (2). These are cases of adult nutritional oedema. The point I wish to make here is this: is this purely an academic finding or has it any practical significance? In Table 14 I have tried to indicate the incidence of myocarditis of unexplained aetiology in South Indian hospitals. In an analysis of 600 cases of heart failure in the General Hospital, Madras, it was found that a high percentage, 14·4%, did not fall under any of the well-established categories; that is, they were not cases of rheumatic, syphilitic, hypertensive, or congenital heart disease. The aetiology is not clear. Some of these cases were



Text-fig. 11. A: Electrocardiogram before and after treatment in a case of kwashiorkor aged 3 years. B. Electrocardiogram before and after treatment in a case of kwashiorkor aged 4 years.



Text-fig. 11. C: Electrocardiogram before and after treatment in a case of kwashiorkor aged 1½ years. D: Electrocardiogram before and after treatment in a case of nutritional oedema in an adult male.

diagnosed as senile myocarditis, some as chronic myocarditis, and sometimes when the clinicians were inclined to be honest they were diagnosed as myocarditis of unknown aetiology. The same finding has been observed in the King George Hospital, Visago, situated in another part of Madras State.

To interpret these findings, I might mention that White & Jones (77), in an analysis of more than 3000 cases of heart failure in the U.S.A., found that less than 2% of their cases failed to fall in any of the well-established categories, so ours is an abnormally high percentage.

Considering that these cases of myocarditis of unexplained aetiology are drawn from the very communities in which kwashiorkor and nutritional oedema are common, I think we can seriously consider the possibility that at least some of these cases are of nutritional origin. Dr Bras has quoted two descriptions of what has been termed nutritional heart disease, and I wonder whether examinations carried out in other areas where nutritional oedema and kwashiorkor are common would not indicate that such cases of unexplained myocarditis are frequent there also.

Table 14. *Incidence of myocarditis of unexplained aetiology in South India*

	Total no. of heart cases	Heart failure of unexplained aetiology
Government General Hospital, Madras (Sanjivi)	616	89 (14·4%)
King George Hospital, Vizag (Ananthachari)	1667	291 (17·5%)

While on this topic, I should like to mention that apart from unexplained cases of this type, we have the feeling that the clinical course and natural history of cases of heart disease of established types such as rheumatic carditis, as we observe them in countries like India, are not the same as have been reported in the West. For example, from the literature published in Europe, one gets the impression that some 80% of cases of mitral stenosis develop auricular fibrillation before they pass on to actual failure, which, according to Dr Sanjivi of Madras, is certainly not true of Indian material. Therefore the background of malnutrition, it seems to me, influences the evolution of other heart diseases as well. I am stating that, not as an established observation, but merely as a point which seems to me well worth exploring.

STUART: Dr Gopalan, these changes that you show are, I think, quite consistent with the findings in beri-beri.

GOPALAN: But the electrocardiographic changes were not reversed by vitamin B_1 therapy.

STUART: Even granted that, the cases you have shown and the age groups you have chosen are not those in which we find typical kwashiorkor; that is, the age group just after weaning. Therefore I think that probably you are dealing with a nutritional syndrome that is different from classical kwashiorkor. We do E.C.G.s on our cases of kwashiorkor here, and we have found no significant changes in the electrocardiogram.

SANTOS: Two Brazilians have made electrocardiographic studies, and they also did not find any major changes.

GOPALAN: I am interested to hear that, but I don't agree that the age group with which I am dealing is significantly different from the age group Dr Stuart mentioned.

CLEMENTS: It is at the upper limit, isn't it?

GOPALAN: Yes. I picked out a few slides which pertain to older cases, but similar abnormalities have been observed in younger children also; on the other hand, one would expect such changes to occur more often in long-standing cases in older children.

BRAS: I am aware that it was not Dr Gopalan's intention to discuss the histology of malnutrition. But the histological changes which he has shown can be found not uncommonly; they are in no way specific for malnutrition.

SÉNÉCAL: I am quite in agreement with Dr Bras, that heart lesions have been found at autopsy—not fibrosis but hyperplasia; this is found in a number of autopsies and is considered to be non-specific.

CLEMENTS: To end this session on the pathology of protein malnutrition, I have asked Dr Bras to give us a summary in much the same terms as we had from Dr Waterlow; namely, 'where do we go from here?'

BRAS: According to the terms of reference given to me as an introductory speaker, I started, as it were, to conduct an autopsy on a protein-malnourished Jamaican child, and exposed some of my findings with the object of comparing them with the findings of others, and then posed the various problems that presented themselves.

As the first, I introduced V.O.D., and as the second, kwashiorkor. The histology of kwashiorkor has been well worked out in many different countries, and there is a wide measure of agreement among histologists. There was little new that we could add, and I decided to give you a cross-section of some less known histological changes found in kwashiorkor, in marasmus and even in some of the so-called subnormal cases who were not acutely ill.

It was argued (i) that we are in great need of a reliable morphologic criterion to judge the severity of the liver damage in protein malnutrition. The amount of fat *per se* does not appear to be important. At present, only the reaction of the parenchymal cells to treatment and the rate with which the fat vacuoles diminish in size are useful criteria for the histologist.

(ii) No morphological diagnostic criterion can be demonstrated to differentiate kwashiorkor from marasmus, except the total amount of fat. This seems to be the only histological difference, and it is a difference only of degree.

(iii) The mode of death in kwashiorkor, especially sudden death, requires further investigation; in view of the reports of hypoglycaemia from various parts of the world, it was tentatively suggested that blood sugar figures and glucose tolerance curves might be studied with profit.

V.O.D. is a condition appearing in Jamaica and India,* leading to acute ascites and, if the condition progresses, to infantile cirrhosis. The importance of the condition for Jamaica can be judged from the fact that Royes(18) saw 200 cases in five years, in a population at that time of one and a quarter million, with a mortality of 35 %; and that Dr Rhodes, in a random study of poor-class children here, found that no less than 47 % of them showed clinical evidence of the condition. The importance for India is already well known.

Dr Dean then inquired about the relation between V.O.D. and protein malnutrition. The answer is at once easy and difficult to give. In kwashiorkor and adult cirrhosis, studies of the relation between the disease and diet have led to the conclusion that a patient lacked certain factors ordinarily supplied by foods containing animal protein or vegetable protein of high biological value. In the same way studies of the background of our V.O.D. patients have led to a similar conclusion, of a similar relation between diet and disease. The matter becomes much more difficult when one tries to explain the aetiology in more detail, but this difficulty, I feel, is experienced equally in kwashiorkor and in adult cirrhosis.

Attention was drawn to the non-portal cirrhosis in V.O.D., leading to a gross picture of Laennec's cirrhosis. In Jamaica and India a proportion of the Laennec's cirrhosis, which hitherto has been dogmatically accepted to be of portal origin, is, in fact, non-portal in origin. This probably holds true for other countries to a varying degree, a fact which has not so far been realized.

It is at this point that I should like to mention the discussions on the sequelae of kwashiorkor, particularly in the liver, a question about which there is no agreement in the literature, so that the subject may even be said to be in a state of chaos. The topic of V.O.D. was chosen to draw attention to a principle and to a theory, which we hope will do something to reduce this chaos to order.

* And as we recently learned, in Egypt(20).

The study of this condition has led us to the hypothesis of a dual aetiology of hepatic fibrosis and cirrhosis. The postulate that two factors are necessary, one being protein malnutrition and the other a different type of injury, either toxic, infectious or parasitic, would, I suggested, help to explain the apparently capricious distribution and variation in type of hepatic lesions in different parts of the world. From a more general point of view, it is necessary to consider the malnourished or protein-depleted organism not as an isolated entity but in relation to other stresses and strains of life, since, more often than not, it is these complex end-results that come under our eyes.

The action of various factors on the body during the state of protein malnutrition is, perhaps, one of the avenues to be explored in the future. We have only just begun to think about the reaction of the protein-malnourished body to ordinary diseases—a fact of tremendous importance for every doctor working in underdeveloped areas. The experimentalists are doing valuable work here, of which I hope more may be described in the course of this Conference.

I do think that much work should be done in the future on children. They represent a state of protein deficiency in a relatively less complicated way. Again, they are available more easily than adults for liver biopsy, a procedure which takes away the burden of histopathologic complications necessarily present when the patient is examined at post-mortem. The biopsy can usually be repeated at least once, and so a further dimension achieved.

Experiments on rats can be of only limited value for deductions about man. Some people hold extreme views on this, and I may remind you of the doctor who said that to apply results of experiments on dogs to the aetiology and treatment of peptic ulcer in man is as scientific as to base a course of post-natal lectures to mothers on a study of the maternal habits of the female kangaroo—a statement to which we know Dr Gyorgy does not subscribe. Neither do I. Notwithstanding major differences between the disease in rats and man, such as localization of fat and fibrosis in different areas of the lobule, the experimental histologist must, I feel, remain on the scene.

A child, admittedly, is not an adult in vest-pocket size and it has its own peculiarities, but everybody surely must agree that the child has been and can in the future be much more of a source from which to draw valuable information. I think that we should urge our colleagues in the many countries where biopsy studies are possible but are not yet being widely done, to use this method and to contribute to our knowledge of the evolution of histopathologic changes in the malnourished individual. I see no objection to paying special attention to the liver for the time being, since the needle biopsy can bring this organ to the surface, so to speak. Subsequent techniques may do the same for other organs, of which we have found during this conference that histopathological details are at present sadly lacking. Until that time, however, we must accumulate increasing amounts of data from the other organs as best we can. These are still insufficient even for such important organs as the heart, the kidneys, and the glands of internal secretion.

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THIRD SESSION

CLINICAL ASPECTS AND TREATMENT OF PROTEIN MALNUTRITION

CLEMENTS: Today we have listed on the programme 'Clinical aspects and treatment of protein malnutrition'. I would suggest that we might separate these, at least for a while, in our thinking and discussion, and that we start with the clinical aspects. This discussion could be the most important aspect of the meeting; it could also be a relative failure.

It would be unprofitable for us to ask the various members who have been associated with kwashiorkor to give us simply a list of the signs and symptoms of kwashiorkor as they know it, or of protein deficiency disease. Dr Waterlow set a different keynote for this discussion in his summary of the first session, when he tried to show that his attempt to analyse the processes that might operate in these conditions, and the approach of the clinician with his picture of the disease as he sees it in the wards and in the villages, are complementary and should reinforce each other. We have an opportunity today of meeting somewhere in the middle of the hill, as it were, where two tunnels are advancing from different sides towards the centre.

I think it will be best to consider separately the various signs and symptoms, and the way in which they differ in different places, trying to see differences in terms of processes. We had a good example of this yesterday in the wards, when the Jamaica group showed us a variety of cases of protein deficiency disease—and took the stand that some represented the more acute phases and others the chronic phase. That was a presentation, to my mind, of clinical signs in terms of processes. I hope that we will be able to think of clinical signs and symptoms today in terms of processes that we know or believe are taking place in the child.

I am now going to ask Dr Rao if he will introduce the subject, and I hope he can do it in that pattern.

RAO: I assume that the only qualification I have to open today's discussion is that I have travelled widely and that I have been associated with the study of various conditions related to malnutrition. Last year I had the privilege of working as a nutrition consultant of the World Health Organization in Burma, and, later, to attend the meeting of the Expert Committee in the Gambia, where the problem of malnutrition in mothers and children was discussed threadbare. There I had ample opportunity not only of presenting our data but also of meeting a number of workers from different parts of the world, and to get their views as well on the problem which we are discussing today. Therefore I shall endeavour to present to you not only my experience but also the accumulated experience of various other workers.

In the field of nutrition research, as you know, the focus of attention has slowly shifted from deficiency of vitamins and minerals to deficiency of protein. There has been intensive activity during the last few years in studying not only the requirements of protein and of amino acids, but the conditions which result from lack of the various factors in the protein complex. That has raised not only new problems but perhaps old ones also; kwashiorkor is one of the problems which has been so activated. A new orientation has been given to a subject which Dr Cicely Williams described years ago. As a result of this, many studies have been published on the question of protein malnutrition, but I shall not attempt to summarize or review all this literature.

Dr Waterlow, who started the ball rolling, faced the brunt of this new technique with which we are experimenting; he gave us a lead, and that has made my task very much easier.

Then on the second day it was with great interest that I saw the pathological processes which may be found in the malnourished child, so beautifully presented by Dr Bras. As one who knows what it is to paint patterns on slides, it has been a pleasure for me to see his paintings.

For this third day I have not come with any prepared notes, because I knew that we were experimenting with a new technique. Even if I had, the Chairman's introductory remarks would have taken my breath away completely. In a way, I am glad that they did. But this is a slight modification of the new technique and, with the permission of the Chairman, instead of having others interrupt me, I propose to interrupt myself at different stages, with this idea—to provoke discussion on the several aspects of the clinical conditions which we are going to consider today.

On this broad basis, we shall take up first the question of clinical signs and symptoms. I have deliberately refrained from using any terminology because I, for one, think that once we come to the question of terminology, we get to the bottom of the sea. We have to consider what are the signs and symptoms that are attributable to protein malnutrition, how far they agree in the several countries where the disease is common, and how far they differ. If they differ, is it due to local variations in the diet or to any other peculiar factors? These are some of the questions which I want to pose to you, so that I can drag you into the conversation instead of your questioning me and probably putting me in an embarrassing situation. After that, perhaps we may be able to define what protein malnutrition is.

We have already had some discussion about the biochemical changes that may be considered specific and the clinical signs and symptoms which are characteristic in a case of protein malnutrition. In conversations between the sessions I have found that all were agreed on one symptom, oedema. Therefore I shall take that first.

OEDEMA

My first questions would be: is oedema invariable in cases of protein malnutrition? what is its onset? Is it generalized or confined to the dependent parts?

Clements: Would the people from Jamaica like to take up the challenge to start with?

Stuart: We see oedema here in two different clinical conditions. One is kwashiorkor, as we define it, and the other is v.o.d. (veno-occlusive disease of the liver). As far as the onset of the oedema is concerned, I do not think we have enough material to be categorical. In some of our cases the history is that the child was well up to some 3 weeks before admission, and then suddenly it developed oedema. On the other hand, the parent might bring the child in and say that the oedema appeared gradually. Usually, in the younger child of about 12 months of age, the oedema at its onset is in the dependent parts, and we find it chiefly in the legs and feet. Older children, in the age group of 2–5 years, usually present us with a history of sudden development of ascites; this is often associated with some oedema of the legs and ankles, but the oedema is overshadowed by the ascites. Occasionally we have recurrent episodes of oedema in these cases.

Williams: On the Gold Coast I noticed that a great many of the mothers took much trouble to look after children well up to a certain age. They were constantly bringing in children of 6–9 months, complaining that they had a very slight swelling of the dorsum of the feet. They would never call it kwashiorkor, but they would look on it as a sinister thing that should be brought to one's notice. Often this slight swelling would persist for a long time before there was any further development. In other cases the oedema would be transient and there would be a stage when you only saw emaciation. Some cases which I put down as cirrhosis would have oedema which was generalized; it depended on how much the child was walking about. But oedema was not specific to any form of malnutrition.

Clements: Is your experience on the Gold Coast in the under-1-year group different from that reported by Dr Stuart?

Williams: I think that my experience would necessarily be different. I was seeing many hundreds of children every day, both sick and well. They were not necessarily sick enough to go to hospital, and I don't think the slight swelling of the dorsum of the foot would be enough to put them in hospital.

Clements: You are implying, then, that you saw cases in a much earlier stage?

Williams: Yes, much, much earlier.

Waterlow: If, when Dr Rao said that everybody was agreed on oedema, he meant that a case of protein malnutrition must present oedema, I would most emphatically disagree.

Rao: I am glad you do.

Waterlow: For one thing, I am sure that we see cases of protein malnutrition without oedema; secondly, if we think in terms of processes, there are so many different factors concerned with the production of oedema. Admittedly, hypo-proteinaemia is a common factor in many of our cases, but many other factors affect water balance or water retention; an example is the work of Dr Gopalan on antidiuretic hormone. Therefore I think it is most unsatisfactory to make such a generalization as you have made.

Scrimshaw: Dr Williams has suggested the same thing when she talked about the cachectic cases. If we conceive of there being a continuous range from marasmus to kwashiorkor, the closer you get to marasmus the less constant would be the appearance of oedema and the more variable the degree and distribution of oedema.

Waterlow: The closer you get to marasmus? Do you mean the lower the body weight, or the more wasting in relation to the degree of protein malnutrition, the less likely there is to be oedema?

Scrimshaw: That perhaps expresses it more clearly.

Rao: I deliberately put this question about oedema because many have agreed, but there is a minority who did not agree, and of those I am one. I wanted to provoke discussion and I am glad that Dr Waterlow has broken the ice. That is one of the main differences of opinion between the various workers—whether or not oedema is a *constant* feature. I, for one, am prepared to believe that in many cases—perhaps we can call them early cases—there may be no clinical evidence of any oedema.

Scrimshaw: Of course, you may get stages in the condition without oedema, although sooner or later oedema is found.

Rao: In fact, you may be slowly walking into my snare. I am trying to evolve a theory which in the end may fit the whole clinical picture.

Clements: What we are looking for are facts, clinical experiences of the conditions which you feel are associated with protein malnutrition.

Aykroyd: May I throw in a second-hand fact here? One of the documents which was presented to the Caracas conference (1) by a group of Venezuelan workers tabulates findings in fifty children with what in Venezuela they are calling kwashiorkor or 'multiple deficiency syndrome'. It is recorded there that out of fifty cases, forty-seven showed oedema. In most cases the oedema was limited to the lower extremities; a few, however, had generalized anasarca. The final statement is that this was one of the first signs to disappear, as soon as the child started taking milk.

CLEMENTS: Did they indicate the nature of onset?

AYKROYD: I think some of the people who know more about the clinical side of the problem in Latin America could take that up.

VAN DER SAR: In Curaçao, you sometimes see the development of oedema within 2 days. The mother will tell you that 2 days before admission the child did not have oedema. Then it develops and is generalized.

CLEMENTS: Referring back to what Dr Williams told us, that the mothers come along complaining of a slight puffiness of the dorsum of the foot, would the mothers in Curaçao have recognized that early degree of departure from normality?

VAN DER SAR: Yes, they would.

CLEMENTS: The recognition of early oedema by the lay person is not easy, is it?

SCRIMSHAW: Your statement is too qualified. Why limit it to lay experience?

WILLIAMS: I have tried to emphasize that my mothers were extremely observant about their children until they were 1 year old.

GYORGY: Not beyond 1 year?

WILLIAMS: Rarely.

DEAN: I agree with Dr Waterlow that oedema is not necessary for the diagnosis of kwashiorkor at any one moment. What we feel in Uganda is that the severe case of kwashiorkor—I am sorry to use that word, but I can't see why I shouldn't; 'protein malnutrition' is a term I have never used—has at some time or other had oedema, although we may not have seen it at the time when the child was admitted. By this, I mean visible oedema. I am quite willing to believe that there is a considerable degree of oedema which is not clinically demonstrable. The oedema in our cases is nearly always the reason why the child is brought into hospital by the mother, and, in carefully questioning the mother, we have come to the conclusion that there is probably some connexion between the first recognition of the oedema and something like an episode of diarrhoea; in other words, the appearance of the oedema may be related to an intercurrent infection or some other cause of illness.

The history of the appearance of the oedema is that nearly always the feet and legs were first involved; in our cases the face is the next part to be involved, particularly under the eyes. We have developed a technique of diagnosing kwashiorkor in our patients merely by looking at the face of the child, who seems to have not only this swelling under the eyes but also a curious bagginess in the lower part of the cheeks. Then, after oedema has appeared in the face, it seems to spread to the hands. We have never demonstrated ascites or any effusion into a joint. The oedema does not appear to have any cardiac or renal cause that we can find, although there is, as you all know, a slight albuminuria. We have never been able to associate that with anything wrong in the kidneys. We do not think that the oedema is due to anaemia. That is as far as I should like to go at the moment.

CLEMENTS: Dr Dean, you said 'at some stage during the course of the illness'. What do you mean by that?

DEAN: I mean that I agree with Dr Waterlow, that the presence or absence of oedema is not essential for the diagnosis of kwashiorkor at any one moment.

WATERLOW: Please, I didn't say 'kwashiorkor'.

DEAN: I'm sorry, but I have become so used to that term. I won't say 'kwashiorkor' when replying to you.

RAO: Suppose you take a hundred cases; how many come into the hospital with swelling?

DEAN: That is surely beside the point. What I have said is that our severe cases, at some time or other, have oedema when we see them, or have a history of having had oedema. We have a kind of case in which there is oedema, possibly gross oedema at one time, and then the child comes in without oedema and in a very bad state. I believe that these may be related to the so-called atrophic cases described by Altmann (2) and by other authors. We have observed cases of this kind in evolution.

PEÑA CHAVARRIA: In Costa Rica we have seen oedema in 45% of our series of 236 cases (3). We have divided it into four grades for clinical information: 1-, 2-, 3- and 4-plus. One-plus is when the oedema is seen only under pressure of the finger on the foot; 4-plus is when it is generalized. The others are intermediate grades. That is the division we have made in order that all the physicians in the hospital can distinguish and classify the oedema.

CRUICKSHANK: Is there ascites when you have 4-plus oedema?

PEÑA CHAVARRIA: Yes, when there is generalized anasarca.

SANTOS: In Brazil I think we see oedema as the most common symptom of the disease. In a report of eighty-two cases, Carvalho (4) found 100% with oedema, which makes it the most common symptom.

CLEMENTS: At what stage in the disease was that recognized?

Santos: Patients brought in within 3 days of the onset of the disease already had oedema: but I believe with Dr Waterlow that oedema is not essential, because we have seen a case of kwashiorkor without oedema. Most often oedema is the main reason for consultation. Usually its onset is related to infection, and it comes on gradually. It generally starts in the lower limbs and, later on, spreads to the face and genital organs. We have seen no ascites, nor have we found any relation between the intensity of the oedema and the seriousness of the disease.

Clements: By 'seriousness' you mean prognosis?

Santos: Progress and death.

Gopalan: In our cases we find that the onset may be either gradual or acute. We find the acute onset particularly in those cases which have had an antecedent attack of diarrhoea. With the cessation of diarrhoea, they come to the hospital with very severe and acute oedema. In those cases in which the onset is gradual and in which you are able to study the evolution of the oedema, we find that it always starts in the dependent parts and then becomes generalized.

We do find the bagginess of the cheeks to which Dr Dean referred, but I don't think it is the result of oedema; probably we can discuss that at a later stage. I confirm Dr Dean's observation that ascites is unusual, but it does occur in some cases with very severe oedema.

Then, with regard to the question of the significance of oedema from the clinical point of view, we find, as Dr Santos has pointed out, that there is no correlation between the severity of the oedema and the ultimate prognosis of the case. We find no correlation between the severity of the oedema and the plasma protein or plasma albumin level, and, what is even more puzzling, we find that there is no correlation between the clinical grading of the oedema and the volume of extracellular fluid as determined by the thiocyanate space. That was puzzling at first, but then, when we talked about it, we argued that, after all, the clinical severity of the oedema will be dependent on two factors: first, on the amount of fluid there is to accumulate, and, secondly, on the amount of space which is available for the accumulation of fluid. The latter, again, depends on the amount of total body solids left behind and the amount of intracellular water. Then, when we tried to test this hypothesis, we found that the clinical grading of the oedema is directly proportional to the product of the extracellular fluid, the intracellular fluid, and the total body solids(5). I think it is necessary to know this, because one often gets the impression that clinicians judge the severity of the case by the severity of the oedema. We have often found that it is the cases which have very acute, severe oedema that respond satisfactorily to treatment. I think that in those cases the oedema is severe, not because there is excessive accumulation of the fluid, but because so much total body solids remain, making the accumulation manifest.

Dean: You are referring to protein malnutrition of young children?

Gopalan: Yes, I am.

Dean: When you mention thiocyanate space, have you measured that in these children?

Gopalan: Yes. We found a lack of parallelism between the thiocyanate space and the clinical grading of oedema, and a correlation with the product that I mentioned, both in the young cases and in the older ones.

Scrimshaw: My previous concurrence with Dr Waterlow and Dr Rao on this matter of oedema was based partly on the kind of cases mentioned by Dr Peña. In Costa Rica and Panama we often see cases of the type that has been called marasmic kwashiorkor; some of them in fact are essentially marasmus, without true signs of protein deficiency. On the other hand, in Guatemala oedema tends to be more frequent and severe. It is a constant feature in hospitalized cases. This may be explained by the fact that these tend to be acute cases—children that have been maintained on a diet that is poor but not terribly poor, until an episode of intestinal infection and diarrhoea occurs. They are then put on an extremely poor diet and develop kwashiorkor relatively rapidly.

Williams: I should like to point out that it is quite unsound to draw conclusions from the condition when a child comes into hospital, perhaps moribund. That is not a fixed point in the development of the disease. My observations are extensive rather than intensive, but during the last year when I was in West Africa there were 17,000 attendances of children in the hospital I was looking after, and only about 800 admissions. During that same period we had 35,000 attendances at the welfare centres which were run by my nurses. Therefore early cases were brought to our attention much more than in many other countries, and the early cases of oedema that I saw were unaccompanied by any other physical signs. The child seemed well, there was no mental deterioration, there was no other clinical sign at all. The mother was worrying about the slight swelling of the dorsum of the feet. Until I saw how these cases developed unless an alteration was made in the diet, I did not realize that this was significant. The early cases were not hungry; they were getting plenty of food. In those early cases I think oedema of the dorsum of the feet was the important sign. Later on, when anorexia set in, then it was confused with hunger oedema. But we are talking about oedema which may be due to several different factors in this disease.

Clements: Has anybody else any experience similar to that of Dr Williams, with, shall we say, 'well-baby' clinics or with children in the community, with respect to this apparently very early sign?

SCRIMSHAW: In one village in Guatemala, when we examined the school children before a demonstration project, we found nearly half of them had minimal but definite oedema on the dorsum of the foot and over the tibia. We were so much interested in this that each one of five physicians evaluated it, and all came to about the same conclusion. Later in the year the oedema had disappeared. Have other people observed minimal oedema on a large scale in school children or pre-school children?

CLEMENTS: You have introduced a new age group here, haven't you?

SCRIMSHAW: The findings just cited were in a group of approximately 100 school children from 6 to 11 years of age living in a rural village.

CLEMENTS: To complete the story, do you get the frank forms or advanced forms of the disease in that group, in your situation?

SCRIMSHAW: Never in surveys in school children, and very rarely in children in the same age group who are not in school, but quite commonly in children of pre-school age in the same area.

WATERLOW: I have no figures to give, as Dr Williams has, but in the past I have examined some two thousand babies at clinics, in the West Indies and in West Africa. These were unselected babies, except that they were attending the clinic. Oedema was most uncommon, compared with three other possible signs of malnutrition—weight loss, hepatomegaly, and red hair.

May I ask Dr Dean to clarify one point? He said, as I understood him, that oedema was always present at some stage in severe cases. But if oedema were not present, would you call it a severe case?

DEAN: I think, if a child dies, it might be considered a severe case.

RAO: Certainly.

WATERLOW: This covers only a very small proportion of children?

DEAN: No; with better methods of treatment, most of our children don't die, but I think we can still recognize a severe case, not only by clinical observations but also by the ancillary methods we have developed. In the history of such cases it is usual for us to find that oedema has played a part, or at least has appeared at some time.

WATERLOW: That I can accept. But what I am trying to get at is this: if a case was mild by all other criteria, but had oedema, would you, perhaps, not classify it as severe? I agree entirely with Dr Santos and Dr Gopalan that oedema in individual cases seems to bear no relation to the prognosis or to the ease of recovery.

BRAS: Dr Dean, have you had any cases that died without oedema?

DEAN: No, but I have had cases who have come into hospital without oedema; these have been very severe cases, which I thought were related to the atrophic cases described by Altmann (1) and others. We have even seen a case proceed from very severe oedema to a stage of no visible oedema.

Cruickshank: And die?

Dean: Some have died and some have not. At first, they did die.

Williams: I think all cases go through a stage of oedema.

Dean: That is what I was trying to say.

Clements: You mean that some of the children had a history of oedema before they came into the hospital?

Dean: Yes. But there is another point, too, in that what *we* call a severe case may not necessarily be what *you* call a severe case.

Bras: What do you call a severe case, Dr Dean?

Dean: That I would rather leave until later when we have assembled some data.

Autret: Most of the cases we have seen in hospital had oedema. Generally the mothers took the child to the hospital because this oedema worried them. In out-patient consultations we were able to pick up mild cases of kwashiorkor with slight oedema, which were brought there because the child had diarrhoea and poor appetite. In all the cases we saw in Central America, only three were without oedema. But it is worth noting that in some places the syndrome is called kwashiorkor when there is oedema, and called malnutrition when there is no oedema. The fact that there is not a constant relation between oedema and hypoproteinaemia is well known. I have seen a serum protein as low as 4·8 g. % and the child, according to the doctor, never had oedema. On the other hand, one can meet a case with oedema without hypo-albuminaemia. The point I want to stress here is that in the early stage this oedema is very mild and does not attract the mother's attention.

Santos: Our observations in Brazil agree with what Dr Autret has just said. In one series of forty-two patients with oedema, seven cases were reported with serum proteins above 5 g. %, and two with proteins above 6 g. %. In several of them also there were high levels of serum albumin, above 2·5, and even above 3 g. %, with oedema.

Burgess: Some workers report the development of oedema after admission to hospital. It may be that acute cases dying shortly after admission to hospital would have developed a transient oedema if they had been admitted earlier and successfully treated.

Clements: There was an outbreak of protein deficiency disease among some Australian aboriginal children last year, following the drought, and about a third of the twelve cases developed oedema after admission to hospital. That was due to bad treatment, because the condition was not recognized.

Sénécal: At Dakar we consider oedema as one of the most important signs of kwashiorkor, but under that heading we are referring to advanced cases and not mild ones. Our description of oedema is more or less identical with that given by Dr Dean. Of sixty-seven cases, fifty-four had oedema of the feet, twenty-six of the face, and fifteen of the hands. We have never found ascites or swelling in the joints. When we studied the onset of the disease by interrogating the mother, it was found that the development of the oedema had been progressive. When it occurs rather rapidly, for instance in the course of 1 week, the protein deficiency has been precipitated by an infection. It is therefore rather difficult to be exact about the mode of onset, but in our opinion oedema of the feet and of the face is one of the earliest signs. We pay a great deal of attention to oedema, and look for it particularly in the out-patient clinics and particularly in relation to the period of weaning.

Rhodes: Concerning the question of oedema and ascites, I have often seen cases of malnutrition who had obvious clinical oedema but no clinically detectable ascites, but when these cases came to autopsy, fluid was found in the abdominal cavity and sometimes in the pericardial cavity, much to my surprise.

McCulloch: I can confirm what Dr Rhodes has said for West Africa, where I was a pathologist for a time.

Williams: I would agree.

Hill: I would like to say something on this, because it struck me forcibly that both Dr Dean and Professor Sénécal mentioned the absence of ascites. You will remember that Dr Dean talked about uncomplicated kwashiorkor. Could we look at it in this way, that in protein malnutrition you do not get clinical ascites; but if you have some complication, v.o.d. for instance or cirrhosis, then you may see the patient in an acute stage with clinical ascites.

Scrimshaw: I think there is some evidence that cases observed in Central America with ascites turn out to have severe cirrhosis or some other complicating feature. I know that is true for the cases studied with Dr Peña in Costa Rica.

Dean: In our cases that died, where we thought there was no ascites, the pathologist could not find ascites.

Clements: If no one has anything more to say on oedema, shall we pass on to the next topic?

GROWTH

Rao: The next thing I should like to discuss is growth—whether, in these cases of protein malnutrition, there is any retardation of growth. If so, to what is it due?

MACKAY: May I ask what is meant by growth to start with?

CLEMENTS: The increments of weight that are measured by a weighing machine. That is what I am talking about.

RAO: We are not going into the principles of basic physiology, but, after years of discussion and experience, we have come to attach some importance of measurements of height and weight in children as indicative of the nutritional status. It is in that practical perspective that we take the matter of growth in relation to malnutrition.

WILLIAMS: May I point out the extreme fallacy of testing children by weight if there is slowly increasing subclinical oedema? Moreover, a large proportion of the children I was dealing with had worms and the weight of the worms altered the weight of the children considerably. I have tested that.

Another thing is that a great many of them have atrophic intestines which are distended with undigested food. That also adds to the weight. Sometimes they have hepatomegaly, and most of my children had splenomegaly, particularly the sick ones. The mere test of weight was therefore no accurate indication of progress.

CLEMENTS: The point is well taken.

GYORGY: Still, did you not find, even allowing for these fallacies, retardation of growth?

WILLIAMS: Not in the early stages when there was only the slight oedema of the feet. They were growing.

GYORGY: But later?

WILLIAMS: Later there was retardation of growth.

MCCULLOCH: May I confirm that? When I was doing nutritional surveys of tribes in West Africa, I started with infants, and I had to discard the weight curves because of these fallacies. But in children of 6 years and onwards I found less variation due to these conditions.

AUTRET: But all these errors that have been mentioned should give a *plus* difference. Generally what we observe is a reduced weight.

MCCULLOCH: Not at all. We found in our clinical surveys that the children in hospital first lost weight and then they began to put it on again.

SANTOS: I think we are very much lacking in data on this subject. That was discussed at the Caracas Conference, and one of the main recommendations of the conference was that such a study should be made, because in the underdeveloped areas very little has been done on measurements of growth and weight gain.

GOPALAN: I entirely agree with Dr Williams about the unreliability of weight measurements in kwashiorkor. We have been faced with this problem, because one gets a very fallacious impression in taking the weights of these oedematous children. Therefore, to arrive at some sort of figures, we have been in the practice of taking minimal weights reached during treatment with a high protein diet.

On treatment the weight goes down for quite a long time; then it remains stationary, and then it starts mounting. We think that the best approximation to 'true' body weight is the minimum weight found in these children after hospitalization. Some of our findings are shown in Table 15.

I know that this is unsatisfactory, but it is very difficult to have anything like a longitudinal study in most of these patients. But I think these figures definitely show that even by the poor standards of growth prevalent in the undernourished communities that we are studying, the cases of kwashiorkor exhibit markedly substandard growth.

Table 15. *Average body weight (in lb.) of cases of kwashiorkor, apparently normal Indian children from the same community, and normal American children*

(Numbers in brackets = number of cases.)

	Age (years)		
	1–2	2–3	3–4
Kwashiorkor	13·8 (40)	17 (21)	18 (14)
'Normal' Indian children	16·8	22	27
Normal American children	26	31	35

RAO: But you are not giving any figures for height.

GOPALAN: I am afraid that we have not yet got many figures for heights. I may have something to say about skeletal development when we take up the question later.

WATERLOW: There is a point about which I feel strongly; it doesn't get us much further to talk about body weights in kwashiorkor without knowing how the patients have been selected. We may prejudge the issue by using this word. Surely a more objective approach is to try and see what association there is of weight loss with other symptoms and signs. For instance, one point on which I have always tried to get figures since I first worked in Jamaica is this: is the loss of body weight less when you have a fatty liver than when you do not have a fatty liver? This is relevant to the question of previous calorie intake and the differentiation between kwashiorkor and marasmus. That is not and should not be a difficult question to answer, but it is extraordinary how hard it is to get data on it. I feel that if, leaving aside terminology, we could concentrate on facts such as the association between weight loss and the presence or absence of other signs, we might get further light on the nature of the syndrome.

Clements: Before I call on the next speaker, would anybody like to take up that challenge?

Rhodes: I have measured the weights of about 600 Jamaican children, both sick and well. I tried to correlate weight with another symptom—hepatomegaly. I found that hepatomegaly was widespread even amongst apparently well children.

I compared the weights of two groups of children—those with and without hepatomegaly—and found that there was a significant difference between them. The children with hepatomegaly were significantly more under weight than those without palpable livers. These figures were summarized in the table I showed in the last session (Table 10, p. 80).

Dean: I would like to comment further on Dr Waterlow's last point, that as we have discussed oedema, couldn't we relate weight loss to oedema? We have, in fact, done a little work on that. We published, in October 1952 (6), the weights of children who were admitted to Mulago Hospital at Kampala, and showed that although nearly all of them had oedema, they were still below what might be called the local average for children of those ages. That is the foundation that you want, isn't it?

Waterlow: Yes, that is the kind of thing I am after.

Clements: A new element has crept in, which I think we would all wish to perpetuate; that is, to relate each new feature, as it comes up, to the ones that have been discussed already, so that we keep on getting correlations. What is the degree of association, as Dr Waterlow says? That is the question we should ask. We might now continue on the subject of growth.

Sénécal: It is necessary to differentiate growth in weight from growth in height. In Dakar we have found that our cases of kwashiorkor are far below the proper weight compared with French children of the same age.

Rao: Is there any normal standard for Dakar children?

Sénécal: No, we do not have such figures. A classification of malnutrition has been established according to the degree of weight loss or weight deficit from normal, grade 1 being 30%, grade 2 being 40% and grade 3 being 50% below normal. This was established by Gomez in Mexico and presented in Cuba, at the International Paediatric Congress.

Rao: Do you think, from the statistical point of view, that this has any significance, if you have no standards in your local area?

Sénécal: This is not my classification but a classification of Dr Gomez's.

Rao: But there they have averages for the local children.

Sénécal: But I want to discuss another point. If you take the heights you will find that the difference between cases of kwashiorkor and the normal is not so evident. This is a point which I discussed with Dr Dean, because when I measure the height of my children with kwashiorkor, I have often found it normal, according to European standards. I was very much astonished at that, but yesterday, when we visited the ward, I think I found an explanation; I saw the Jamaican cases, and they are very young. I think that when you have kwashiorkor in very young infants of 6 or 7 months, growth is so quick that the difference between the normal and the pathological is much clearer and greater than later, at say 18–22 months, when the growth curve is flattening off. I wonder whether it is not possible, by relating the weight or the loss of weight to the height or the loss of height, to make a differentiation between the various clinical groups; in true kwashiorkor the loss of weight in relation to height would be less than in so-called marasmic-kwashiorkor, where you would have a greater loss of weight with relatively normal height.

SCRIMSHAW: We have data from birth up through school age on several thousand children in Central America. It may clarify things if I could show three figures which also relate to the point raised by Dr Rao, whether cases of kwashiorkor should be compared with European or with local standards.

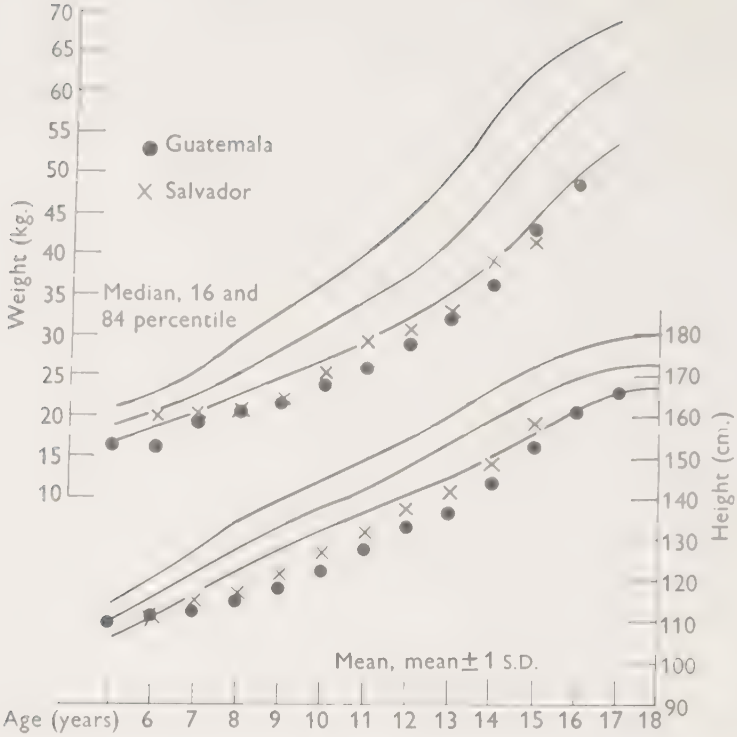
Text-fig. 12A shows the median and the 16 and 84 percentiles for weight, and the mean plus or minus one standard deviation for height, for boys in the State of Iowa, U.S.A. Most of the children plotted are in the public schools, both rural and urban. The El Salvador average values all fall below the United States 16 percentile, which makes them approximately 2 years retarded compared with the United States children. The Guatemalan children—and this figure includes data on a predominately rural group—fall approximately 3 years behind. Of course, this means that many individuals are much more than 3 years retarded.

Text-fig. 12B shows the same thing for girls. Retardation of these magnitudes is also observed in Honduras, Costa Rica and Panama.

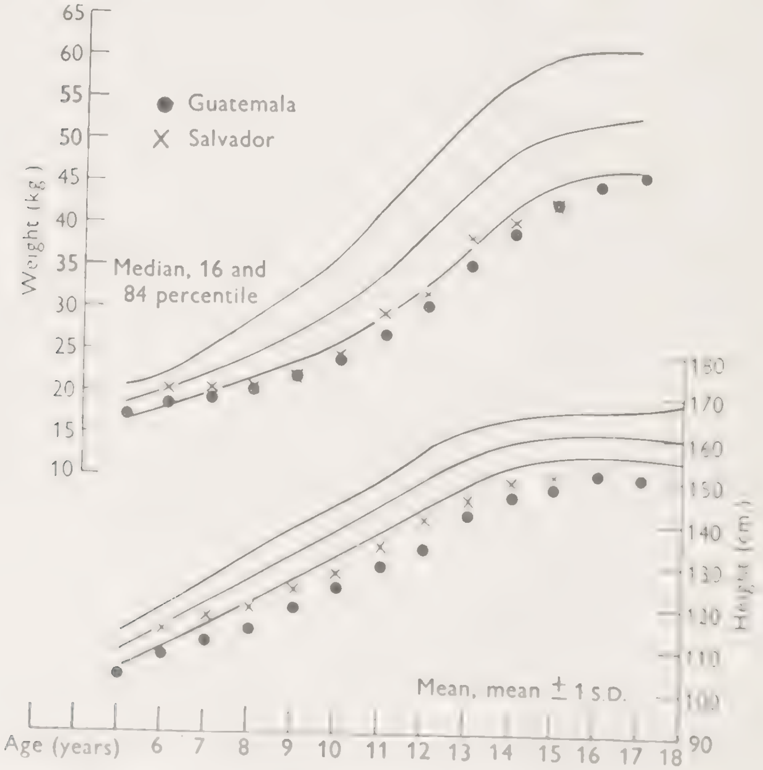
Although not shown in these figures, we have a considerable number of heights and weights of children between 1 and 5 years, and the picture is very much the same. At approximately 1 year of age the observed height and weight values begin to separate out from the American curve. Age being comparable, would we be justified in evaluating kwashiorkor cases, in Guatemala for example, by the American standards? We think that perhaps we are since it does turn out that children of Guatemalan parentage in private schools in Guatemala fall close to the median line determined for the United States. The distribution of data is so similar to that for Iowa school children, that there seems to be no reason why we should not use the United States standards.

GYORGY: Is that the same genetic group as the kwashiorkor cases?

SCRIMSHAW: No, the private school children are not quite the same



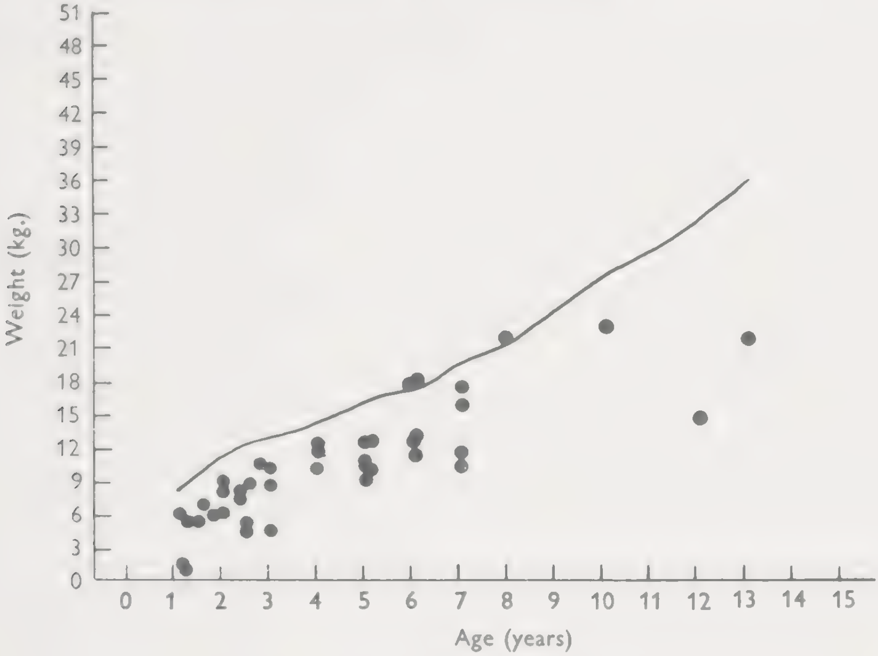
Text-fig. 12 A. Growth in boys. The solid lines represent boys in Iowa, U.S.A.



Text-fig. 12 B. Growth in girls. The solid lines represent girls in Iowa, U.S.A.

genetic group as the one in which kwashiorkor is prevalent, because there is more Europen admixture in the children in the private schools. However, in comparing rural groups in El Salvador and Guatemala with the same blood group distribution (approximately 90%, type O), the children in Guatemala are considerably behind those in El Salvador in development. This suggests that environmental influences are playing a greater role than genetic ones.

Text-fig. 13 is taken from the report which was prepared by Autret & Behar (10), and shows their plotting of approximately fifty cases of kwashiorkor against the present Guatemalan rural growth curve. This Guatemalan curve is already well below one standard deviation from the mean for United States children, as given in Text-fig. 12, so that these cases are being compared with children already greatly retarded. Every case falls below the curve.



Text-fig. 13. Weights of central American children with kwashiorkor compared with the weight curve of Guatemalan children.

Do you have any further comment on that, Dr Autret?

Autret: I wish to add that the figure also shows the distribution of cases of kwashiorkor according to age. As you can see, there are quite a number over 4 years of age.

Cruickshank: Did these cases of kwashiorkor recorded there have both oedema and enlarged liver at the time the weight was taken?

Autret: This was the weight taken just on admission to hospital or the day after. All except three had oedema. Most of them did not have a marked enlargement of the liver.

Scrimshaw: The point is that, despite their oedema, the majority of these cases of kwashiorkor are a year or two retarded in weight compared with children already 2 or 3 years retarded by North American standards. It seems that in Central America at least, growth retardation, already very prevalent, is more marked in kwashiorkor.

Dr Gyorgy asked about genetic differences in the groups. I think that strong evidence of the greater importance of environmental than genetic factors in determining average growth rates in Central American children is the fact that these children do respond with increased skeletal growth to supplementary feeding or to supplementary vitamin B_{12} or aureomycin, as will be discussed later.

Gyorgy: Do you mean the so-called normal children, or cases of kwashiorkor?

Scrimshaw: I mean school children without kwashiorkor. Guatemalan children, 3–4 years behind the United States standards, do respond significantly, which they would not do if the limitation of growth were primarily due to genetic factors.

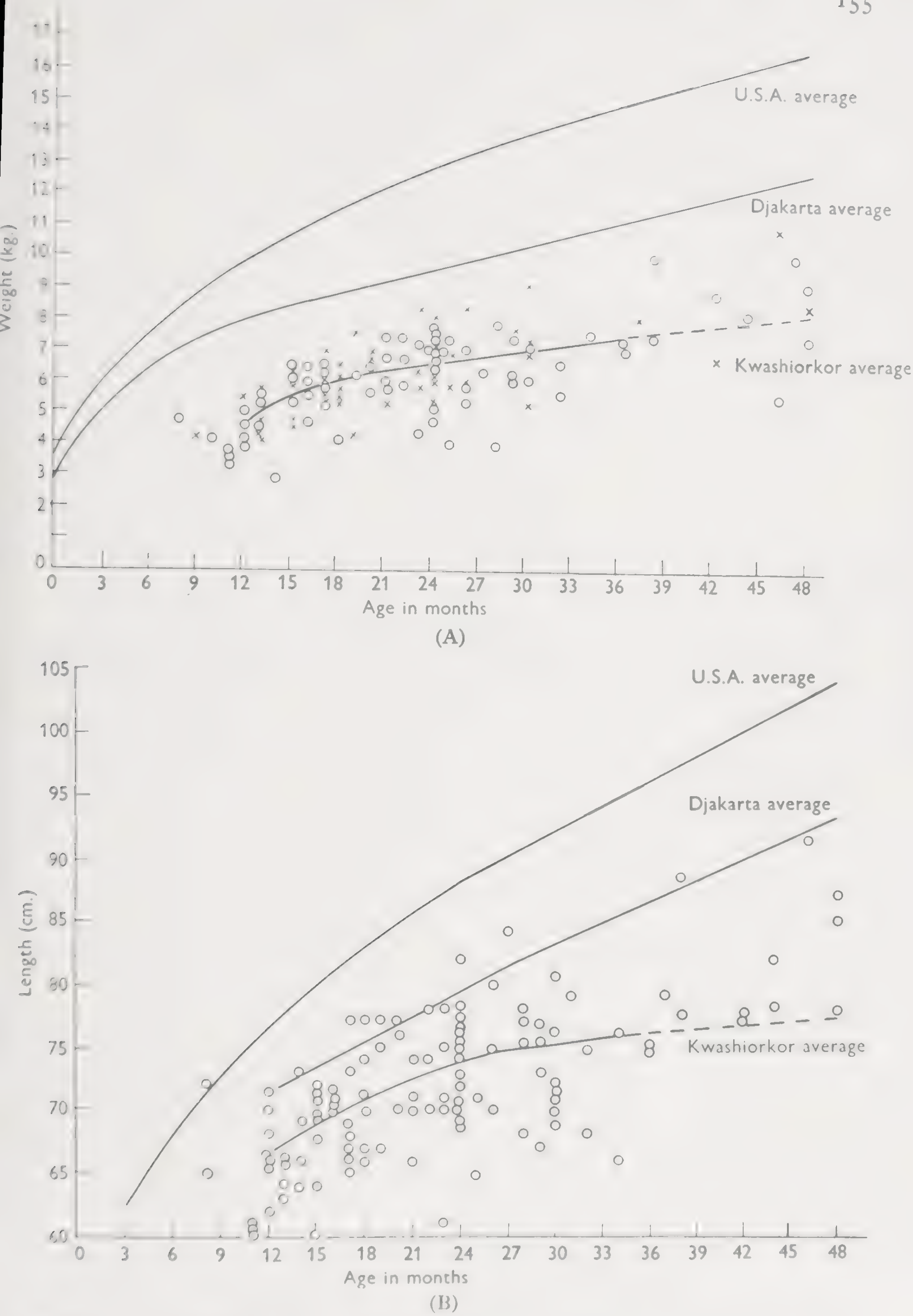
Burgess: Dr Oomen, W.H.O. consultant in Indonesia, has constructed growth curves of average Indonesian children and of children with kwashiorkor. He had over 100 cases of kwashiorkor, and both their heights and weights are significantly lower than the Indonesian average (Text-fig. 14) (7).

Autret: The height seems to be less affected than the weight.

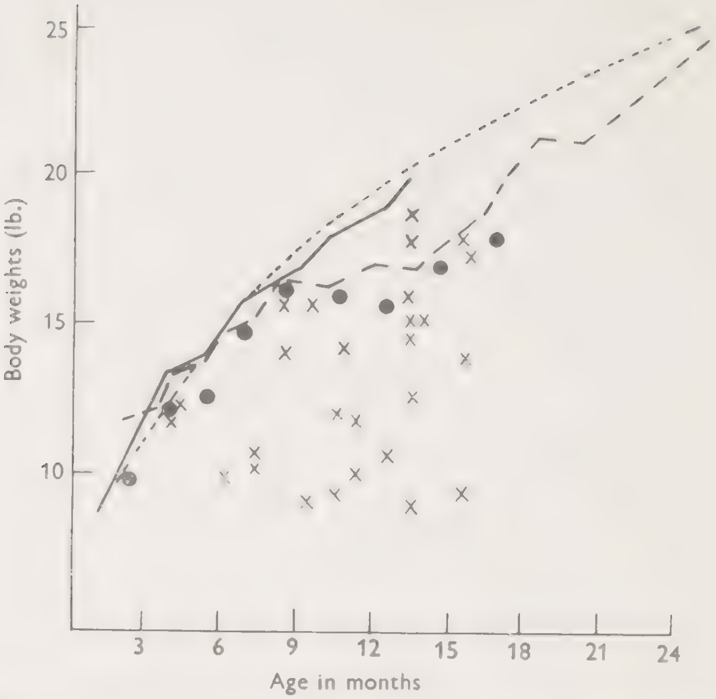
Sénécal: The distribution of heights, it seems, is not as regular as that of weights. You have more cases of normal height.

Van der Sar: In Curaçao we took the weights of the children with kwashiorkor at the moment when they were at the lowest point of weight in hospital. We then calculated the average weights of apparently healthy babies in outdoor clinics. We weighed 100 babies who were just 1 month old, another 100 who were just 2 months old, and so on up to 13 months. The curve that we got in this way from 1200 weights (Text-fig. 15) closely resembles the United States 10 percentile (Text-fig. 15). The figure also shows the normal according to Dr Waterlow's publication (Text-fig. 15) (8, 9). The cases of kwashiorkor only occurred between the ages of 5 and 22 months. You will see that their weights, at the moment when they have lost their oedema, fell far below the normal curve.

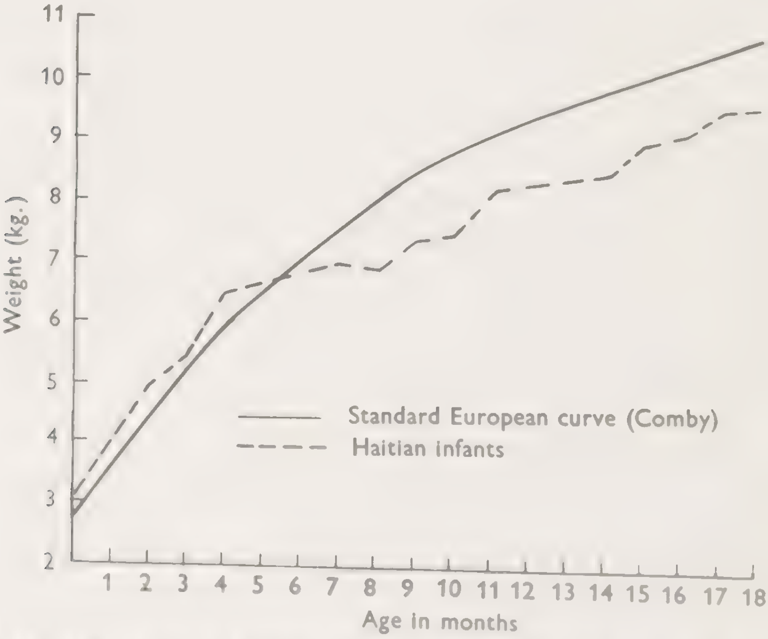
Waterlow: May I just say, Dr van der Sar, that my curve is not meant to be a normal curve, but the average of some 1000 apparently well, West Indian babies.



Text-fig. 14. A: Body weight in 125 kwashiorkor cases, Djakarta 1952. B: Body length in 125 kwashiorkor cases, Djakarta 1952. (Reproduced by courtesy of Dr H. A. P. C. Oomen, and of the World Health Organization.)



Text-fig. 15. Bodyweights of normal infants and of cases of kwashiorkor in Curaçao, N.W.I. Weight curve: ——, body weight of infants, as recorded in various clinics in Curaçao, 1,200 observations; – – –, Jamaica weight curve (from the figures of Waterlow) 8); - - - -, U.S. 10 percentile of Holt (quoted by Waterlow); ● ● ●, patients with fatty liver in Jamaica; × × ×, patients with fatty liver in Curaçao. (Reproduced by kind permission of the editors of *Documenta Neerlandica et Indonesica de Morbis Tropicis*.)



Text-fig. 16. Growth curve (weight) of 100 children studied in the M.C.H. centre 'De La Saline', Port-au-Prince, Haiti. (By kind permission of Dr C. Boulos.)

Autret: Here is a similar weight curve from Haiti (Text-fig. 16).

Dean: Obviously the suggestion of Dr Sénécal's of relating weight loss to loss of height is an extraordinarily valuable one, and we should do our best to follow it up. But there is one statistical point over which we shall need some help: to be 20% under weight may be bad, but to be 20% under height may be absolutely dreadful. When we were investigating German children, we found in mildly undernourished children that there might be a loss of 10% of weight, as judged by American standards or by pre-war German standards, but that those same children would be only 2 or 3% under height; so I think we must bear in mind that to be a small amount under height may be as serious as to be a large amount under weight.

Clements: It is a very important observation, and I think there is a growing feeling that it is more reliable to relate body weight to height than to relate body weight to age.

Gyorgy: I may add, however, that it is not a new observation. It is 50 years old.

Clements: Oh, yes. I said 'a growing feeling'.

Burgess: We have some figures from Venezuela; of some forty-two cases, 89% are described as being under weight, while only 25% had abnormal statural growth.

Clements: But there is no correlation between the two?

Burgess: No.

Rao: One point at this stage, when we are discussing the question of height and weight, is whether there is anything specific to the disease we are studying—whether this retardation in growth and height is specific to kwashiorkor or protein malnutrition, or whether it is a general observation in other conditions of malnutrition and deficiency disease.

Clements: Dr Rao, we might pose that question in respect of all the signs and symptoms. I am sure you would agree that nobody will suggest that oedema, for instance, is specific to kwashiorkor?

Rao: But we have to consider groups of symptoms and signs which you might finally say are specific or are probably the most important as far as diagnosis is concerned.

Hill: I think the point is well taken. All this morning the question of oedema has been discussed. We have been throwing a large net and we have probably been talking about a hundred different conditions. I think it is time the point was brought up, what are we talking about?

Clements: This Conference is on protein malnutrition, and I think it would be a pity if we did not bear in mind that there may be many environmental factors or dietary factors which are going to produce variations on this theme. I think a good many of us have in our minds at least a doubt whether there is such a thing as pure protein malnutrition; that what we see clinically are cases in which the dominant theme is protein malnutrition and that there are local variations in signs and symptoms brought about by an overplay or a variation in the theme, caused by deficiencies of one or more of half a dozen nutrients, and the combination and permutations of these are going to affect the signs and symptoms. Unless we are prepared to throw out a broad net and bring in all these variations, I think we are going to end up where we were in the Gambia—trying to talk about a disease which it is doubtful exists.

[General agreement was expressed.]

SKELETAL DEVELOPMENT

Clements: If there is nothing further on growth, we might take up bone development as an aspect of growth.

Gopalan: We have carried out some studies on the development of the bones of the wrist in normal subjects and in a few cases of kwashiorkor. I must say at the very outset that these studies are still at a preliminary stage, but I thought it might be of some interest to present these observations, incomplete as they are. Pl. 19 (1) shows the X-ray of the bones of the wrist in a normal child, aged 3 years and 10 months. You find that all the bones are present except the navicular; the capitate, the hamate, the lunate and the epiphysis of the radius are all there. This is just to indicate that in normal children, as we see them in India, skeletal development proceeds according to the standards accepted elsewhere.

Pl. 19 (2) is from a child of the same age, 3 years and 10 months, and here you find only two bones—the capitate and the hamate—which normally should appear by 3 months, and the epiphysis of the radius, which usually appears by 1 year and 6 months. This is just to indicate that there is a wide divergence between the chronological age and the skeletal age in this case of kwashiorkor. In Pl. 19 (3), even the epiphysis of the radius has not appeared.

McCulloch: What age is this?

Gopalan: The same age, 3 years and 10 months. In Table 16 I have tried to indicate the results obtained in ten cases of kwashiorkor, and to compare them with the results in eighteen normal children. We find that seventeen of the eighteen normal children had a skeletal age which corresponded to the chronological age. There is only one child who showed some evidence of retardation. But of ten children suffering from kwashiorkor, only two had the skeletal development that would have been expected for their age. The other cases had varying degrees of retardation, ranging from 6 months to 2 years.

I do not suggest that these observations are by any means specific to kwashiorkor. We have observed the same findings in cases of undernourished children who did not present the clinical features of kwashiorkor. I am not even certain whether these changes reflect protein malnutrition, considering that the diets are deficient in calcium as well as in protein. I am just presenting this to show that in kwashiorkor, as we see it in India, there is evidence of retarded skeletal development.

Table 16. *Retardation of skeletal development in children suffering from kwashiorkor*

	Total no.	No. whose skeletal age corresponds to chronological age according to American standards	No. whose skeletal age is below the chronological age by		
			6 months	1 year	2 years
Normals	18	17	—	1	—
Cases of kwashiorkor	10	2	3	1	4

McCulloch: Were the two children in the kwashiorkor group who had normal skeletons less ill than those who were definitely retarded? Is there any correlation?

Gopalan: No, I don't think there is any correlation between the extent of skeletal retardation and the severity of the kwashiorkor.

Dean: This is fascinating to me, because we have done wrist X-rays of about a hundred children, and have come to the conclusion that there is possibly a slight retardation in bone age in a group of children whose average age is about 18 or 19 months, but that it is very slight; we must do much more work before we can be sure of it. We have nothing at all comparable to yours. On the other hand, I think that we have no evidence of calcium or vitamin D deficiency. Dr Sénécal, I believe, has some.

Sénécal: I have never found any retardation of ossification but only a decalcification of the bones observed radiologically.

McCulloch: We saw the same kind of thing in West Africa, though we could not do radiological studies. The children began to recover the minute they started running around naked in the sun. Obviously this was a vitamin D effect. I am wondering whether Dr Dean's observations do not have a bearing on the same fact.

Clements: Dr Gopalan, would you like to answer that, having particular reference to the quality of the bones? I think you will agree that the quality of calcification and the structure of the bones in the cases of kwashiorkor that you showed are very different from the normal.

Gopalan: We were playing with the idea that density studies might give us some information, but after a few trials we gave up attempts to pursue them because, particularly in the adult, we noticed that there are evidently two factors which influence bone density in opposite directions. I think that point has been brought out well by McCance and his colleagues (161). There is demineralization of the bone, which tends to make it more transparent, and on the other hand there is a depletion of fat, which probably makes it more opaque. These two factors work in opposite directions, and I think the results of densitometric studies for that reason are apt to be fallacious. I know there is a great deal of attention being given to the use of ivory standards by which to relate bone density to nutritional status, but personally I am not inclined to be very enthusiastic about densitometric studies.

Stuart: We have X-rayed the wrists of all our cases of kwashiorkor, a total of about sixty, and also of about twenty-five children of the same age group admitted to the wards for other reasons. We have found no difference in the X-ray pictures in these two groups of cases.

McCulloch: What ages were they?

Stuart: Mostly from 1 year to 18 months.

Dean: May I ask Dr Gopalan, what is the bone age of those children you showed, Pl. 19, who were 3 years and 10 months old but had retarded development?

Gopalan: I wouldn't like to say. I wouldn't like to impart any exactitude to assessments of skeletal age.

Dean: But surely their bone age is of the order of 6 months?

Clements: Oh, no!

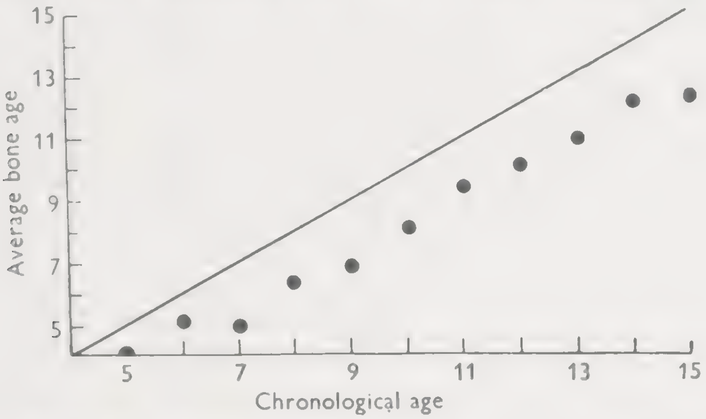
Gopalan: Why 6 months? The epiphysis of the radius has appeared. That appears only at 1 year and 6 months. There is one child, though, who showed only the capitate and the hamate. This could easily be assessed as 6 months, since by the third month you expect those two bones to appear.

Dean: My point is that if bony development had only reached the age of 6 months, then when did the kwashiorkor occur which caused retardation? In fact, were you getting development up to 6 months in the bones, and then getting kwashiorkor? Or was there something else at work?

Scrimshaw: Perhaps our observations from Central America may shed some light on this point. In the same groups for which we have just shown the height and weight retardation (Text-fig. 12), we also have bone age studies of some 500 children. In El Salvador they were on the average nearly 2 years retarded in bone age compared with United States standards; in Guatemala they were nearly 3 years retarded in bone age compared with the United States standards of Greulich & Pyle (11). The findings in the Guatemalan children are illustrated by Text-fig. 17.

CLEMENTS: But that is an older age group, isn't it?

SCRIMSHAW: Yes, this is principally the 6–11 year age group. In Guatemala, at least, rural school children are slowly slipping further behind in bone age. We do not, unfortunately, have in our group many cases of kwashiorkor, but we did do a survey of a thousand children of all ages in El Salvador for rickets. Of that thousand, only three turned out to have changes which could be identified with rickets. Two of these were children under 1 year of age, protected from the sunlight because they were sick.



Text-fig. 17. Bone age deficit—Guatemalan school children, rural Indian villages. Solid line: United States standard (11); points: average bone age of Guatemalan children.

The physician who studied them believed that they also had kwashiorkor. Their bone changes were not only those of rickets but showed complications that were somewhat baffling to the radiologist.*†

PEÑA CHAVARRIA: In our Costa Rican cases we see changes in the bones —not only retardation of growth but also osteoporosis. Sometimes in those children, who are re-admitted from time to time with malnutrition, we can see a mark on the X-ray picture of the bone—the same mark that we sometimes see in the hair. But we will talk about that later on.

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* These 1000 films have since been evaluated for bone age along with similar films from Honduras by Dr Martin S. Wittenborg, radiologist of the Children's Hospital of Boston, during his visit as W.H.O. consultant to I.N.C.A.P. He finds that the retardation begins on an average soon after weaning and in these countries develops almost entirely during the pre-school years. Children of school age in El Salvador and Honduras do not usually drop further behind in bone age and may even regain part of their loss relative to United States standards.

† The two cases reported by Dr Scrimshaw are unusual since it seems that rickets and kwashiorkor seldom exist together, even in countries where both diseases occur. Presumably this is because the specific changes of rickets only develop under the stress of growth. Of interest in this connexion is the observation of Dr Estella Budiansky (12), that in cases of rickets in Brazil the elevation of plasma alkaline phosphatase is much less than in rickets in Europe and the U.S.A. Perhaps this is because enzyme production is limited by marginal protein malnutrition, not severe enough to produce kwashiorkor or to stop growth entirely.—(Editor.)

CLEMENTS: Yes, lines of arrest of growth.

SCRIMSHAW: Pl. 20 shows the wrist of a boy who is 9 years old, with a bone age of 3. Although this is a rather extreme case, we have a few others with even more marked retardation.

CLEMENTS: We accept the fact that there can be, in any community, retardation of bone growth. What we are trying to do is to see what is the relationship of retardation of bone growth to protein deficiency disease. Can anybody help us on that point?

SCRIMSHAW: I think the fact that these children do respond to supplementary feeding with vegetable or animal protein, with a gain in bone age out of proportion to the elapsed time—that is, they will gain more than 1 year in bone age within 1 year—is pertinent to the problem.

DEAN: No, it is not, because that will happen with children who are merely mildly undernourished in a general way. In Kampala, we have, side by side, an Indian community and an African community. The African community has a great deal of kwashiorkor. In the Indian community there is a great deal of rickets and a great deal of retardation of bony development of a kind we do not see in the African community.

MACKAY: Up to what age is bone age related to body growth? Bone age should be a very useful index.

SCRIMSHAW: Changes in bone age, of course, parallel very closely retardation in height.

MACKAY: Yes, and the weight?

SCRIMSHAW: There are so many factors that influence weight that there is no necessary parallelism.

CLEMENTS: I think we might move on at this stage. Dr Rao, would you introduce the next subject?

CHANGES IN THE SKIN

RAO: The next sign which most of us are interested in discussing is changes in the skin. Most workers have described a dry skin which has lost its lustre, to which they give names such as 'crazy pavement'—all of you know what that means. There may be certain other changes, such as exfoliation at the folds, either in the elbow or the groin. This was very prominent in the cases I saw at Dakar.

What I would like you to discuss is this: How far are these specific for protein deficiency? As you know, skin lesions are commonly seen in vitamin A deficiency. Clinically, there is a dryness, and histologically a hyperkeratosis. In cases of kwashiorkor there is one peculiar feature, apart from the generalized dryness of the skin. That is the changes which have been described so well in the African child, limited to the skin-folds.

I should like you to discuss at length whether these have any significance, whether they have any local variations, or whether they are only an accident.

STUART: In Jamaica we do not commonly see the florid skin lesions that are described in other places; the skin changes are usually minimal in our cases.

RAO: Will you kindly explain what you mean by 'florid skin changes'?

STUART: When you have gross exfoliation and the skin peels off, leaving underneath red, raw-looking areas which are sometimes spread over the whole body. We see these only occasionally. But when they are present, in our cases at any rate, they do not have any relation to the prognosis.

CLEMENTS: Have they any relationship to the other two signs, oedema and weight loss or growth failure?

STUART: They are usually found in the child that has oedema rather than in the atrophic marasmic type of case.

CRUICKSHANK: Is there any relation to the degree of oedema?

STUART: Yes, I would say the skin lesions occur in the cases which have the most oedema.

RHODES: I think that Dr Stuart was talking about cases in hospital. We have found that Jamaican children living at home and apparently well, whilst never showing any desquamating skin lesions such as are commonly described in kwashiorkor, very often had skins which were dry, wrinkled, atrophic and 'mosaic'. What relation this bears to dietary insufficiency, I don't know. But generally speaking, throughout the country, there is definite protein undernutrition and definite skin changes in otherwise healthy children.

CLEMENTS: Would you summarize those changes that you see in community surveys?

RHODES: The mildest change we see is dryness affecting mostly the shins and upper arms. A slightly more severe change is 'wrinkled' skin which feels dry and slightly scaly, but shows no change in pigmentation. A third type is 'mosaic' skin which is dry, glazed and shows cracks.

CLEMENTS: Are you inferring that one is a progression of the other?

RHODES: Possibly.

CLEMENTS: Is there any particular distribution of the last two?

RHODES: The shins are the most commonly affected, but I have seen it on the face, in the butterfly distribution, on the forehead, and also on the abdomen.

CLEMENTS: Is there any one age which is more affected than another?

RHODES: I have seen it most commonly in school-age children, but also in younger ones, of pre-school age.

CLEMENTS: What is the youngest age at which you have observed this?

Rhodes: Below 1 year.

Mackay: In the age group that I have studied, which is roughly from 7 to 15 years, we find about 40% of the children have a dry skin; it goes into the cracked stage in approximately 8%

Sénécal: In Dakar the skin changes are seen in very great intensity. They can be classified into certain categories. The most common is depigmentation, which begins in the face and in the folds, such as the inguinal region. This is not only the most common but also the earliest change. The next sign is hyperpigmentation, which begins on the external surface of the limbs. The epidermis becomes black and desquamates like a piece of paper. The dry desquamation is also common and severe in the inguinal region. Finally, there is a form which seems to be peculiar to Dakar, and that is the development of serous bullae in the epidermis, with desquamation following, as after a burn. Crackled-skin, as described at Kampala, seems also to be one of the most common forms. I saw in Cuba, first-hand from Dr Gomez, cases which are directly comparable to the Dakar ones, and also cases in Haiti which were the same.

Scrimshaw: Because we are dealing with a different racial group and because the skin lesions are, perhaps, a more severe and constant manifestation than in most places, I should like to show photographs of one case in Central America. In the general examinations of school children we find almost constantly xerosis and follicular hyperkeratosis, but we do not find hyperpigmentation of the skin, nor lesions suggestive of pellagra. This is of interest because of the very large amount of corn in the diet, which is pellagra-producing in other areas. In the cases of kwashiorkor, on the other hand, hyperpigmentation of the skin is an almost constant feature and is very often intense.

Pl. 21 shows a severe case of kwashiorkor in the rural town of Sumpango, which died soon after hospitalization, despite treatment. It is a 5-year-old girl, who at the time of admission weighed 11·2 kg. and measured 89 cm. in height. This photograph shows well the generalized hyperpigmentation and desquamation of the skin of the entire body.

Peña Chavarria: I think it is very interesting to note that in certain areas of Brazil, as Dr Vergara informs me, you do not find so much hyperpigmentation or desquamation, and that is probably attributable to the absence of corn or maize in the diet. In areas where corn plays a very small role in the diet we find much less hyperpigmentation.

Scrimshaw: That was the implication of my earlier remarks, that these people are probably on a borderline diet in respect to niacin. Although in general signs of niacin deficiency are not common in kwashiorkor, this deficiency may play a role in causing the skin manifestations.

WILLIAMS: Pellagrous lesions can be cleared up simply by protection from the sun; they are photosensitive. Kwashiorkor lesions cannot.

WATERLOW: May I put forward a clinical impression to be knocked down? That is, that these skin changes are more common in cases of protein malnutrition which are less under weight, and are rare in the marasmic type of case, as Dr Stuart said. Again, I should like to make a plea for collection of data on the incidence of these lesions in relation to body weight. We made some such observations in Brazil(13) but we haven't enough cases to show anything significant.

GOPALAN: We find that in some 50% of cases of kwashiorkor the skin is clinically quite normal. In roughly 25% it is dry and scaly, and in 25% there is a dermatosis, which is generally of the 'crazy pavement' type.

CLEMENTS: By 'crazy pavement' skin, you mean—?

GOPALAN: The type of skin lesion which starts as jet-black patches over certain localized areas. Then these black patches exfoliate, leaving depigmented skin bordered by a hyperpigmented margin. The lesion occurs over the perineal region, the pressure sites and the flexures. I think that much confusion surrounds the terminology of cutaneous manifestations; 'crazy pavement' dermatosis, a name which was originally applied by Dr Williams to the type of lesion which I have just described, is applied, I think wrongly, to the condition which should be called 'mosaic' skin, which is predominantly localized on the antero-lateral aspects of the legs. I do not think there is any difference in the distribution of this 'crazy pavement' lesion between the cases which Dr Sénécal described and the cases we see in India. The pressure sites and the flexures are affected in both groups.

There is another type of dermatosis which we see in certain cases of kwashiorkor. This is a peculiar type of punctate, pinkish pigmentation, found on the antero-lateral aspects of the legs; the skin in these cases is quite smooth. I have not done any pathological or histological studies of this; maybe these spots are evidence of perifollicular haemorrhages, and that is as much as I can say about it. I would like to know whether others have seen such cases.

VERGARA: A symptom has been described by a paediatrician in Bogotá(14), which I think may be relevant to what you have just said. In several of a small series of kwashiorkor cases purpuric spots were observed. Also, in Venezuela(1) I have heard it mentioned that the prothrombin time was prolonged in fifteen out of sixty cases of kwashiorkor.*

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* Caruana and his colleagues in Tunis(15) described purpuric spots in some cases of kwashiorkor. Bleeding time, clotting time, and prothrombin time were normal. The appearance of these spots was not prevented by vitamins C or K, and was regarded as a sign of ill-omen.—J. Waterlow.

GOPALAN: Thank you Dr Vergara. Coming to the point raised by Dr Waterlow, from my experience I do not think there is any correlation between the occurrence of dermatosis and the severity of the disease or the degree of under-weight status; nor is there any correlation between the incidence or severity of oedema on the one hand, and the occurrence of dermatosis on the other. We have had a few cases with no oedema, showing maximal dermatosis. The incidence of dermatosis in a series of cases studied in Madras City by Professor Achar is very much higher than with us at Coonoor. If I remember right, in his cases over 80% exhibited dermatosis. On the west coast of India also, in Malabar, we find that the incidence of dermatosis complicating kwashiorkor is fairly high. I do not know the reason for this discrepancy, but perhaps I might mention that in our city the evidence of vitamin B complex deficiency is minimal. Only 40% of cases which we investigated in Coonoor exhibited the oral lesions of B complex deficiency. On the other hand, in Professor Achar's series and in the cases seen in Malabar, B complex deficiencies are more common. I wonder whether the higher incidence of dermatosis in Professor Achar's series may be related to this? I also saw, in Professor Sénécal's photographs of cases which exhibited dermatosis, that there were signs of B complex deficiency.

CLEMENTS: Dr Gopalan, before you finish, can you help us? I think that Dr Rhodes helped us considerably when she gave the picture in the community. Can you give us a comparable picture from any Indian community studies?

GOPALAN: The type of dermatosis which is very common in Indian children, as I see them in Coonoor, is a condition which, for want of a better term, we call folliculosis. In this condition you get a peculiar prominence of the hair follicles. I won't call it phrynoderma because there are no horny plugs surmounting these follicles. We do see phrynoderma as well in some cases, but these are generally in an older age group. In these younger children of the poor communities dryness and scaling is the most prominent abnormality of the skin. Dermatoses of the type I have just described are also seen. Other types of skin lesions are relatively rare, in Coonoor at any rate.

CRUICKSHANK: I would like to ask Dr Gopalan if, in the cases he is recording, the diet is essentially or purely based on rice as the source of carbohydrate?

GOPALAN: Yes.

CRUICKSHANK: Are any of the other observers here seeing cases which are receiving purely a rice diet, or are they seeing cases which get maize as well as rice as a source or carbohydrate?

RAO: That is an excellent point which you raise.

Aykroyd: There would be, Dr Gopalan, a difference in the diet between Malabar and Coonoor, would there not?

Gopalan: Yes. In Malabar they may take more tapioca than they do in Coonoor. But I don't think that there is any appreciable difference between the diets consumed in Coonoor and the diets consumed in Madras City.

Rao: Professor Cruickshank is hinting at the possibility of a relation to maize consumption; isn't that right?

Cruickshank: Yes. As far as I can gather from the discussion, Dr Gopalan's cases show fewer instances of skin changes or a lesser degree of skin change than any of the others reported so far. Now, does anyone else see cases of kwashiorkor where there is no maize or very little maize in the basic diet?

Sénécal: Yes, we do in Dakar.

Williams: I have seen cases of kwashiorkor in non-maize-eating areas, for instance Malaya.

Vergara: In the Amazon region, where the diet is based mostly on manioc with almost no maize, we saw very few cases which presented the typical picture of kwashiorkor. Less serious cases of protein malnutrition are more common.

Cruickshank: Without the skin changes?

Vergara: Yes, some cases without and others with only slight skin changes.

Sénécal: In Dakar the basis of the diet is millet, not maize. We have tried to treat both the skin lesions and the mucocutaneous ones with vitamins of the B complex—B_1, B_6, B_{12}—without any result so far. However, they recover very quickly when they are on a high protein diet.

Autret: I have a picture of kwashiorkor in Ceylon where the staple food is rice. It shows exactly the same skin lesions as those seen in cases of kwashiorkor who receive a maize diet.

Burgess: In Indonesia 10–20% of cases are described as having dermatosis.

Clements: Yes, but what is the diet?

Burgess: The diet is rice.

Clements: How much dermatosis? Is it very advanced?

Burgess: I think it is not so severe as the dermatosis seen in some of the cases that have just been described.

Dean: We have a very severe dermatosis, almost exactly the same as that described by Dr Sénécal, in children who, as far as we know, have never received any maize at all throughout their lives.

Clements: Here in Jamaica skin changes are not very prominent. Do they get maize?

STUART: Yes, cornmeal is a major component of our diet.

SCRIMSHAW: Nearly all the speakers have mentioned dry skin, or xerosis. That is probably associated primarily with a deficiency of vitamin A. I wonder if we might be getting off the track by putting too much emphasis on niacin and other members of the B complex? Is not xerosis a more common forerunner?

DEAN: We do not see xerosis.

SCRIMSHAW: Are your diets relatively deficient in vitamin A?

DEAN: No, I don't think they are.

SCRIMSHAW: And yet you get hyper-pigmentation?

DEAN: Yes, very severe in the type of dermatosis described by Professor Sénécal.

WILLIAMS: On the Gold Coast, where an enormous amount of maize is taken, we see dry skin occasionally, but a great many of the frank kwashiorkor cases are getting some vitamin A (in red palm oil).

SANTOS: There is some evidence that the skin changes are less common in the white than the black skin. For instance, in eighty-one cases reported in one study in Brazil (17), it was found that lesions were present in 84 % of the cases with black skin, but only in 46 % of those with white skin, and in 75 % of the mixed.

GOPALAN: May it not be that this is a social factor? It may be that the white people are getting more food and more nutrients.

SANTOS: We don't think there is any relation to the economic condition, because most of them belong in the same socio-economic stratum.

PEÑA CHAVARRIA: In Costa Rica white people predominate, and we see the changes in skin colour very frequently in them as well as in those with dark skins. Therefore I do not think there is a racial factor. I have found, though, that it is easier to detect the change in colour in white than in pigmented skins.

CLEMENTS: Would I be simplifying the matter too much if I said that it might be possible to relate the skin appearance to a dietary pattern? In other words, that you more frequently get advanced or severe skin changes on one kind of diet than you do on another kind of diet?

AYKROYD: I don't think that that conclusion could be drawn from the discussion so far.

CLEMENTS: Well, then, I am being provocative, and my summary is not correct. Is there any further discussion or comment on skin changes?

WATERLOW: The question has been raised about the treatment of these skin lesions with niacin, and my reading of the literature is rather conflicting on the results. I would like to know whether it has been found successful or not by other people.

CLEMENTS: Niacin alone?

WATERLOW: Yes, I would like to know whether people think that the skin lesions respond in any way specifically to nicotinic acid.

DEAN: I have the assembled evidence from the literature, which suggests that attempts to cure the disease as a whole with nicotinic acid have not been successful. Dr Trowell was one of the people who tried it. But there is some evidence that skin lesions which are usually considered to be associated with nicotinic acid deficiency may clear up when nicotinic acid is given, without affecting the general condition of the patient. That, of course, is reasonable, if you postulate that not only is there an element of protein deficiency but also an element of vitamin deficiency, and that the vitamin deficiency specifically acts on the skin.

WATERLOW: But other people have not confirmed that, have they? In Brazil the paediatricians in several places told me that they found no benefit whatever to the skin lesions from nicotinic acid, compared with a high protein diet. I thought that Professor Sénécal might confirm that.

DEAN: The evidence is conflicting, but there are several reports in favour.

SÉNÉCAL: The lesions of the skin are not improved by treatment with nicotinic acid.

CLEMENTS: That means nicotinic acid alone?

SÉNÉCAL: Yes, alone, without high protein. With high protein, they were improved and cured within 10 days.

SANTOS: I should like to point out that perhaps this is also a question of the age of the lesion. It happens that old lesions are not influenced by nicotinic acid, but the early lesions are.

DEAN: The lesions certainly clear up on a high protein diet, as Dr Sénécal has said, without the addition of nicotinic acid.

SCRIMSHAW: But your high protein provides tryptophan in excess, so it might be in part a response to 'niacin' therapy, as if niacin were added.

CLEMENTS: And if the high protein diet is a skim milk diet, doesn't it also provide some niacin?

DEAN: Not very much. But the tryptophan is probably the important point.

McCULLOCH: We are talking all the time of a high protein diet. May I ask, has a pure protein been used, casein for example, alone?

DEAN: No, never.

McCULLOCH: Then we are begging the question.

DEAN: It is a very expensive and difficult piece of investigation, which has to be done some day.

McCULLOCH: What is the difficulty?

DEAN: The difficulty and expense are in the preparation of pure casein.

RAO: It is not a very pleasant thing to give, either.

WILLIAMS: I would like to point out that the skin changes in pellagra are due to photosensitivity of the skin, but that does not apply to kwashiorkor.

DEAN: That is an important point, which Dr Williams was the first to make. She also, in 1934, noted that there is a difference in the distribution of the skin lesions in kwashiorkor and pellagra (18).

MCCULLOCH: Some people originally called it infantile pellagra, didn't they?

DEAN: Yes.

SCRIMSHAW: I might add that the cases they still call 'pellagra' in some of the paediatric wards in the general hospitals in Central America are kwashiorkor with skin pigment changes and not pellagra at all.

CHANGES IN THE HAIR

CLEMENTS: Does anyone want to comment on the changes in the hair?

RAO: May I summarize what has been done, so that we can discuss the differences, if any? Most of the published work has described certain changes in the hair. Everybody has agreed that it is dry and perhaps loses its lustre; sometimes there is alopecia and the hair is lost. But the specific change which has been reported is this, that there is a certain amount of depigmentation and a certain discoloration, that has been described by the African workers as a coppery red, I think. What do you call it?

SÉNÉCAL: Yes, red or coppery red.

RAO: Either coppery red or, in milder cases, a sort of rusty brown. What I would like to know is, whether this discoloration and depigmentation are specific. Are there any subtle differences in the changes in the hair as far as protein malnutrition is concerned, and, if there are differences, to what are they due?

PEÑA CHAVARRIA: This is one of the commonest signs we see in our children. My impression is that the changes in the hair are connected with protein or amino acids and not at all with the vitamin B complex, because we gave our children, in one of our experiments, the different B complex components, with no effect at all.

SCRIMSHAW: Is it not true, Dr Peña, that you get cases in hospital with pale hair, and then, after treatment with a high protein diet for 2 or 3 months, you get a band of black hair? After they have gone back home to their original conditions, they are likely to come back in a few weeks or months in nutritional failure once more, with a band of white hair growing out. They may have several alternate bands of black and white hair, representing alternate periods of treatment and poor diet in the home.

Peña Chavarria: Yes, that is so. I can show you some pictures (Pl. 22), of the stripes corresponding to the nutrition of the patient at different times. The first (1) is of a girl aged 7, who had been admitted to hospital 10 months before with a typical multiple deficiency syndrome. The other picture (2), shows the same thing in a baby. The blackest zone corresponds to the period when the child was in hospital. In our experience the hair grows faster in the well-fed baby. The difference is more or less this: the rate of growth in a well-nourished baby is from 10 to 12 mm. a month, and in a very poorly nourished child it is from 7 to 9 mm. per month. You can see exactly when the baby was in the hospital; it was 5 mm., or 6 months, ago.

Scrimshaw: This is known as the 'flag sign' from the description by Dr Peña Chavarria and Dr Saenz-Herrera in 1948 (19).

Mackay: Has any attempt been made to measure the weight and the composition of the hair in these conditions?

Autret: Very little. The work is just starting now. In Tunis, Dr Hertetz is studying the hair pigment in children with kwashiorkor.*

Gyorgy: Did not Professor Platt show something of that kind in the Gambia, indicating an abnormality in the pigment which is produced during kwashiorkor? (20)

Autret: Yes.

Gopalan: In 40% of the cases of kwashiorkor which we deal with, we see these hair changes, particularly discoloration; I mention this because some statements have been made that in kwashiorkor, as it is seen in India, hair changes do not occur. We see these changes also in children not exhibiting the signs of kwashiorkor—just undernourished children.

Cruickshank: May I put a rather theoretical question to the paediatricians? Do you see changes in the hair like this in chronic illness in children, where protein malnutrition can be excluded?

Williams: Yes.

Peña Chavarria: Yes, and not only in children, but we see it also in adults. I can show you a picture of a woman who had acute malaria, who was vomiting for 2 weeks, and you can see the colour of the hair changing during that period of time.

Cruickshank: I think that my question is a very difficult one because any severe prolonged illness may, of course, produce protein malnutrition, and it may be impossible to answer that question and exclude protein malnutrition as a factor.

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* J. Garrow in Jamaica (unpublished observation) has found that red hair from undernourished babies has a cystine content averaging 11%, compared with 15% in normal hair. (J. Waterlow.)

PEÑA CHAVARRIA: Well, I don't know if my case was suffering from malnutrition, but she was vomiting the whole time. As soon as she was put on the normal diet the natural colour of the hair came back again.

BRAS: What you meant was a deficient protein intake, Professor Cruickshank?

CRUICKSHANK: No, not necessarily.

DEAN: Deficient absorption, rather. In coeliac disease, alterations in the hair have been described.

GYORGY: In other words, secondary protein deficiency.

AUTRET: It might be well to note here the studies that have been made on hair texture in sheep, according to the sulphur intake. Excellent experiments have been done, especially in Australia, on the growth and texture of the hair and its sulphur amino-acid composition (21).

CLEMENTS: Is there any correlation between these hair changes and the other signs we have discussed?

DEAN: We have the impression that there is not a good correlation, that the hair changes may be related to the length of time during which the child has been exposed to protein malnutrition, and not to the severity of the condition as we see it at one particular moment.

WATERLOW: I feel that hair changes are one of the most common signs once we get away from cases in hospital. Jelliffe did a survey in a number of villages here, and although there was a variation in the incidence, he found, taking the overall average, that about 50% of unselected children and infants had red hair. Again, in the Gambia we used to see it very commonly in the villages, as I think Dr Gyorgy will agree. The picture one gets there is of a child who has red hair, dry skin, is under weight, and possibly has hepatomegaly. Putting together such facts as one can, I believe, like Dr Chavarria, that the hair changes are associated with protein deficiency rather than with any vitamin deficiency.

FACIES

RAO: The next sign which we may discuss is facies. Yesterday we saw some cases presented to us in the wards. The typical cases of kwashiorkor showed a puffiness of the face or bagginess of the cheeks, in contrast to those labelled marasmus, where the facies has a sort of pinched appearance. I wonder whether you would consider these as different stages of the same condition, as far as the facies is concerned, or whether both of them are quite different; whether you can find a child at some stage with a pinched appearance of the face, and, at a later stage, see the same child with puffiness or swelling of the face? I just pose the question, so that we can discuss it further.

GOPALAN: Yesterday Dr Dean referred to what he called 'bagginess of the cheeks' in babies with kwashiorkor. We also have been struck with this abnormal swelling and prominence of the cheeks in kwashiorkor. I don't think it is just a question of preservation of subcutaneous fat, because in these cases the swelling is abnormal, it is excessive. I find the same condition also in other children who do not present the oedema and dermatosis or the other features of kwashiorkor, but who show signs of undernutrition in the form of stunted growth. I have therefore been interested in the question of the pathogenesis and significance of this bilateral symmetrical swelling of the cheeks. The condition can be so exaggerated as to justify the designation 'moon face' in some of these children.

CRUICKSHANK: Is that apart from obvious generalized oedema?

GOPALAN: Yes. I want to emphasize that I have seen this condition in children without oedema. I think that most paediatricians are familiar with it. It is nothing new, but it has been completely ignored because it is so common. I remember I mentioned this finding to Dr Williams when she visited us some 2 or 3 years ago, and she suggested that it was due to worms. We do find evidence of heavy roundworm infestation in some of these cases, but it is not invariable. Moreover, a heavy load of roundworms may be found in children who do not have 'moon face'. Therefore I am not happy about the infestation hypothesis.

We have tried to treat some of these cases with various nutrients, including vitamin A, and we find, on following the improvement with caliper measurements, that the treatment which definitely brings down the swelling is skim milk. Of course, that will not equate it with protein deficiency.

Pl. 23 shows a case before treatment, and again after 4 weeks of treatment with skim milk. The caliper measurements show a distinct diminution, of about an inch or so, in the width between the cheeks. I don't have any clear-cut views on this; I am just putting it to you because it is a condition which we see very commonly. The one invariable accompaniment, as I said, is evidence of stunted growth.

HILL: Was there any erythema of the face, or any rash?

GOPALAN: No, nothing.

DEAN: Do those happen to be children in whom you made measurements of the total body water, or of extracellular fluid volume?

GOPALAN: Not in these children. I have done body water measurements only in cases with oedema, some of whom had this puffiness also.

DEAN: Nevertheless, they might have occult oedema, might they not?

GOPALAN: I don't think it is due to oedema because the configuration of the swelling does not support the oedema hypothesis. The swelling should be maximal in the dependent portion if it is due to oedema. Actually we find the centre of the sphere much higher. A condition somewhat similar has been described as the result of ACTH therapy, and it has been suggested that it may be a manifestation of increased hydrophilia of the connective tissue, in which case you will not get the swelling maximal in the dependent portion. All I can say is that this condition is associated with undernutrition, and responds to skim milk therapy.

RHODES: The few cases of muscular dystrophy which I have seen in children seem to have the same sort of rounded, perhaps dependent, appearance of the cheeks. I wonder whether it may not be due to the same cause in kwashiorkor, a hypotonia of the facial muscles.

AUTRET: I have seen a case in Haiti showing exactly the appearance described by Dr Gopalan, but with slight oedema, I think. It was cured after 2 weeks in hospital on a high protein diet.

SÉNÉCAL: I think we see the same thing in Dakar.

DEAN: It has struck me that just as you can diagnose a cretin by its face, so you can almost diagnose kwashiorkor, at least when it is severe, by the appearance, whatever its geographical position.

AUTRET: The name 'bouffissure d'Annam' was given to the syndrome in Indochina because of this moon-face (22).

RAO: There was a statement by one of the delegates this morning that there is nothing that skim milk does not cure, including this moon-face!

CRUICKSHANK: We saw a child in the ward last week, who was not admitted specifically for kwashiorkor, but who almost certainly was suffering from protein undernutrition. She had two very definitely palpable masses in the cheek—rounded, smooth masses, which could have been glandular, in the parotid, if only they had been farther back. I would like to hear somebody comment on this pad, presumably consisting of fat, which was very discrete and easily palpated.

DEAN: Is there any anatomical structure in that region that might be affected?

GYORGY: I think that is the sucking pad that I was talking about; all other subcutaneous fat has lost its consistency and the water content of the surrounding tissues has probably increased. The fat appears more prominently in the sucking pad. That would be my guess.

HILL: Sucking pads pulling at an empty breast?

GYORGY: Well, they try hard, you know.

DEAN: But, in our cases, as Dr Davies has so often pointed out, there is not a complete loss of subcutaneous fat, because the fat on the abdomen is largely retained, and I would expect it to be retained in the face too. But it is quite possible that there is a localized loss.

GYORGY: That perhaps could be hypertrophy.

DEAN: Yes, it could be.

WATERLOW: When you speak of caliper measurements, Dr Gopalan, do you mean across the face or through the cheek wall?

GOPALAN: We have done both measurements, but the 1-inch diminution to which I was referring was the whole width of the cheeks. We have used the calipers devised by Keys for his subcutaneous fat measurements. I don't have the figures here. In any case, I have not got a large series.

DEAN: There is one other point. Circumoral pallor is a constant feature in our cases, and has been described in other parts of the world. Has anyone else here seen a notable circumoral pallor in the face of a child with this disease?

STUART: I have seen it here, but not in every case diagnosed as kwashiorkor.

ONSET

RAO: I shall now go on to consider the onset of the disease, because that has a bearing on some of the other symptoms we are going to discuss. Is the onset acute and sudden, or is it insidious? Are there differences in the different parts of the world where the disease has been described?

WATERLOW: One thing that has struck me, Dr Rao, is that whereas in Africa, as everybody knows, weaning is rather late, in Jamaica and in Brazil it occurs a good deal earlier, on the average between about 6 and 9 months. Yet when I was analysing the figures for the age at which cases were presented at hospital I found that the average age and the age distribution that Dr Vergara and I observed in Brazil and which all the Brazilian writers have recorded were exactly the same as in Africa, according to Trowell's data. In other words, in spite of the earlier weaning, there seems to be a lag period before the development of the disease to the stage at which the patient comes to hospital.

CLEMENTS: You infer that the child in Africa who is retained on the breast secures a significant amount of milk. Is that valid? When we talk about weaning in different communities, are we aware of the fact that the child may suck at the breast and get nothing? To say that a child is weaned at 15 months in one community, and in another is weaned at 9 months, is to imply that the first child was getting breast milk for 6 months longer than the second. Are we justified in making that assumption?

WATERLOW: You made the assumption, Dr Clements, not I.

CLEMENTS: No, I drew the implication, because you left it there for me to draw.

WATERLOW: If you pressed me further on this point, I would say that in the Gambia, where weaning is late, as in East Africa, we made measurements of 24-hour milk output from mothers, as far as we could. I am sure that Dr Dean would agree that it is a very difficult thing to do, and the results cannot be more than approximate. At the age in which we are interested, from 1 year to 15 or 18 months, we estimated that the milk output was of the order of 15–20 ounces a day; that is to say, by no means nothing. Now, against that, we did not find florid kwashiorkor in the Gambia.

RHODES: Often people will tell you that in Jamaica infants are breast-fed for quite a long while. In point of fact supplementary feeding starts very early, between 2 and 3 months. Infants are partially breast-fed up to 9 months or even to 1 year. This means that they receive porridge and another source of milk during the day and breast milk in the night. In ten or twelve cases I have tried to determine the quantity of breast milk available to the baby, because it seemed to me that an infant which requires, after three to four meals a day, another three to four feeds during the night, must be hungry. I could not do 24-hour samples, but I tried to express milk before a feed was due. I found that the total amounts expressed from both breasts were, in all the cases, very small. I remember in one case it was half an ounce from both breasts. Therefore I have come to the conclusion that as soon as the Jamaican child is on this system of partial breast feeding, breast feeding can actually be discounted.

VERGARA: If I may clarify this point a little more, I have a series of case-histories of children suffering from protein malnutrition whom Dr Waterlow and I saw in Brazil. It appeared that these babies had been weaned at 3 or 4 months of age. In practically all the cases the mothers stated that some supplementary foods had been given because their milk was diminishing rapidly. However, the amount of food given, as described by the mother, was rather small and of low nutritive value.

AYKROYD: Was it complete weaning at such an early stage? They got no more mother's milk after that point?

VERGARA: In many of the kwashiorkor-like cases observed, it was found that when the powdered skim milk distributed by U.N.I.C.E.F. was given daily to the child, breast feeding had apparently been completely stopped, even when the skim milk was obviously insufficient not only to provide the required protein but also from the point of view of calories. The shortness of the lactation period was confirmed by several paediatricians in the towns visited. Early weaning, according to them, was frequent not only in the poor but also among the well-to-do classes of the population.

SCRIMSHAW: In Costa Rica, as well as in the rest of Central America, it is generally stated that children are not weaned until 1 year, or after. In a survey in the rural areas of one community (31), 37% of the mothers were no longer nursing their infants at 6 months and 13% were unable to breast-feed at all.

McCulloch: Aren't we getting off the point as far as the onset is concerned?

Clements: I am not so sure that we are. I have been asking myself that question, and I came to the conclusion that, surely, the relation of weaning to onset is important.

Williams: In many of the tribes on the Gold Coast the babies can be breast-fed by any of the women of the same family. When the baby is first born, he is handed around the compound and suckled by most of the women there. Many of them go on lactating for a long time. The record was held by a grandmother who had not had a child for 19 years. The grandchild survived to get kwashiorkor, was brought to the hospital and it was my first case that was cured. Many of them suckle other babies in the compound at moments of stress, and in nearly all of them I could express some milk; that is, a great many of the women had secretion of milk even though they had not had a baby for some time. Therefore, you cannot guarantee that there has been no milk given to that child. Some babies get kwashiorkor when they are still on the breast. But the fact that they get this disease shows that the breast milk is insufficient or inadequate.

Gyorgy: But when you say 'some secretion' what was the quantity? Only a few cubic centimetres?

Williams: I'm sorry, I did not have an opportunity to measure it.

Sénécal: In our district breast feeding is continued for quite a long time, and it is remarkable to find that most of the cases of kwashiorkor develop within 2–3 months after the cessation of breast feeding. Of sixty-four cases, fifty-seven presented between 18 and 30 months of age, and there were only three younger than 18 months, of which one was less than a year. Two of these three cases showed the pathological signs of fibrocystic disease. There were four cases over 3 years old. I think, therefore, that the weaning period is extremely important, for three reasons: first, because the infant thereby loses a supply of easily assimilable protein. It is difficult to state precisely what the protein production of the African mother is during the second year of lactation. At the moment we are in the process of collecting and analysing milk; I think that the breast milk may contain a total quantity of 3–4 g. of protein a day, consisting of amino acids which are directly assimilated.

The second factor which comes in is that at the age of about 18 months the child begins to walk about and so may become infected with parasites. A third factor which has been emphasized by Dr Carothers (14) is that whereas up to the age of about 15–18 months the child makes a slave of its mother, from then on the mother abandons it, dumps it on the ground, and it passes from being the master to being an object of no interest to its parent.

In trying to analyse the onset of the disease, the first sign which we frequently find, and which has been emphasized by other authors in Dakar—Raoult, Bergeret (25) and others—is diarrhoea and anorexia.

CLEMENTS: It would seem from the comments on weaning that there is a good deal of confusion, largely arising out of lack of information about the quantity and, perhaps, the quality of milk that is obtained by infants who suck at the breast, and that we have been inclined to look upon the removal of the child from contact and access to the breast as synonymous with cessation of the supply of milk. But that may not be so. More information is required on this particular point, if we wish to know the relationship of breast feeding to the onset of the disease. Does anybody have any facts that would relate the onset of the disease to any change in the weight curve?

WATERLOW: In Brazil I have seen weight curves in two cases which showed a stationary weight for about 5 months before the onset of symptoms.

GYORGY: Do you think this period was the onset of the protein malnutrition? You may get the same flattened curve in infants who are breast-fed but who have an insufficient amount of breast milk and no supplement—in other words, infants who are generally undernourished.

WATERLOW: Lasting as long as that, several months?

GYORGY: Oh yes.

AYKROYD: One would imagine that if one could look back into the past of these cases, from the point at which they arrive under medical care, probably the first sign is just that—a falling-off of the weight curve. That does not help very much, because there is no conceivable way of collecting information of that kind about clinical cases.

SCRIMSHAW: But almost all children in an underdeveloped area will show this kind of falling off. After 10 or 12 months of age the growth curve begins to flatten off; but would it help to pick out the worst of them?

WATERLOW: You remember the curves that Dr van der Sar showed (Text-fig. 15). The Jamaican curve of so-called normal babies has a definite flattening between 9 months and 18 months or more. I suggest that in babies who develop kwashiorkor there would be an earlier flattening which went on longer, with perhaps even a fall before the onset of the disease—the same pattern as in the average baby, but intensified.

DEAN: I intend to refer more definitely to this subject in my discussion of epidemiology tomorrow, but I think it is worth mentioning that Dr Hebe Welbourn (46), who has been working in clinics outside Kampala, has noticed this slowing down of the rate of weight-gain to which you refer.

She has followed a few children who have showed this, and found that they went on to develop the signs and symptoms of kwashiorkor, which brought them to hospital.

Clements: Has she been able to find similar curves showing the same flattening, in children who have not gone on to develop kwashiorkor?

Dean: I don't know.

Clements: You see, that is the point that has been made by Dr Scrimshaw, that this flattening is a more or less common occurrence; but only a few of the children end with kwashiorkor.

Cruickshank: Dr Welbourn, then, was following a number of cases before there was kwashiorkor, and was able to see it develop?

Dean: Yes. She thinks she can detect a pre-kwashiorkor stage.

Cruickshank: What are her criteria for diagnosis?

Dean: Failure to gain at the accepted reasonable rate is one criterion. Another is changes in the hair—again, a very doubtful sign. If I may say so, I am a little disappointed that this conference has not so far got down to a definition and further discussion of the very mild case of kwashiorkor, which, to my mind, involves very great difficulty; in fact, I think it was Dr Waterlow who said, on the first day, that the very severe case of kwashiorkor is easy to diagnose, but the other lesser states are very difficult to be certain about.

Clements: Well, this is your opportunity, Dr Dean. We are asking for the signs of onset of the disease.

Dean: We have given this matter a considerable amount of thought. It seems to be very difficult to say anything definite about it. I think that we would first put cessation of growth, or at least the slowing down of growth. Secondly, as I said before, a tendency for a change in the texture and colour of the hair. Thirdly, some failure of the skin to maintain its glossiness and brightness and complete blackness. Fourthly, the early development of an unsuspected anorexia.

I say this because whenever people have tried to measure the actual intake in calories of children with kwashiorkor, they have been surprised at the low calorie intake. Under Professor Holmes a very small survey was done in the neighbourhood of Kampala, in a village where Dr Hebe Welbourn has been conducting a clinic for some time and not, therefore, a completely unspoiled village from the point of view of observation. The few children whose diets could be accurately measured certainly had a much lower intake of calories than was expected (26).

Autret: At what age?

Dean: They were at the kwashiorkor age as we see it in our district—between 1 and 3 years old.

Gyorgy: At what stage of the disease were these measurements done? At the onset?

Dean: No, these were children who could not be described as fit for admission to hospital for kwashiorkor, but Dr Welbourn thought they showed a tendency in the kwashiorkor direction. You will understand that what we want is something more definite, and we have nothing more definite. We thought that perhaps we might get some information from biochemical tests, but so far work on that side has only begun.

Clements: Has anyone else, like Dr Dean and his colleagues, seen kwashiorkor in the process of development?

Cruickshank: Did you do any liver biopsies on the cases in this pre-kwashiorkor group?

Dean: No. They were all children in their homes, who did not come to hospital, but were seen only in the clinic.

Clements: Dr Williams, your earlier remarks suggested that oedema was the first sign. Could you add to that?

Williams: I think that it is one of the first signs. Certainly, at the time when the oedema presented, there was no complaint of anorexia, and there was no sign of malnutrition. The children were well fed and happy, and they seemed to be normal children except for the swelling of the dorsum of the feet. I should therefore put that as one of the very early signs, although other cases might start differently.

Cruickshank: When you saw this early oedema of the dorsum of the feet, without any other symptoms or signs, did you follow some of the children through and see them develop kwashiorkor?

Williams: Yes. Not knowing there was anything sinister, the mother would come up and say, 'His feet are swelling', and I would say, 'Well, the child seems extremely well otherwise; I don't think there is anything to worry about. Come back again.' She would come back the following month, and it would be early or perhaps advanced kwashiorkor.

Cruickshank: A month between the first time when oedema was noted and the appearance of skin signs and anorexia?

Williams: Yes. There was not time enough for the hair changes to develop, except a loss of gloss on the hair and skin, but at that stage there were none of the well-marked later changes.

Bras: Dr Dean, what kind of a village was it in which the observations you mentioned were carried out? Were the children investigated in any other way also? I mean, could there possibly be a reason for them to develop anorexia apart from just their protein malnutrition? Were there any signs of helminth infestation or malaria or any other disease?

Dean: Those things were certainly present in that village. Dr Hebe

Welbourn thought she could observe a continuous process which starts in the village in the way I have described and in many cases ends with the child having to be admitted to hospital.

HILL: Can you tell us when this process seems to start? How long has she had them under surveillance before they develop kwashiorkor?

DEAN: She is able to see them from birth onwards. They grow magnificently for a period, which I should think was probably 4½ months in her cases. We have all of us seen magnificent children at the age of 4½, 5 or 6 months, weighing some 21 lb. It is not until after that time that this slowing down in the rate of growth seems to begin.

HILL: Professor Sénécal mentioned that his cases of kwashiorkor were about 18 months old, and Dr Dean tells me that there are no young babies who have kwashiorkor in his area, whereas here in Jamaica some of the kwashiorkor cases are much younger than 18 months. What is the reason for this difference?

SÉNÉCAL: Weaning is later in Africa.

DEAN: There are cases which we have seen, and which other people have described, in which kwashiorkor in a florid form has occurred well below the age of 18 months. If we speak of 18 months, it is an average figure. We have, all of us, seen cases starting under a year, but nearly always, I believe, it has been possible to trace some connexion between the onset of the disease and a lack of milk in the diet. I shall have more to say about that tomorrow. By milk I mean human milk or cow's milk.

AYKROYD: We have been talking in terms of onset. These cases in this village would be a group which, right through the period of weaning up to 2 or 3 years of age, shows at a very mild, non-clinical level, signs of retarded development—the same signs that in certain instances lead to kwashiorkor?

DEAN: Yes, I think that is almost certainly so. I am only trying to give a simplified picture of Dr Hebe Welbourn's idea of a continuous process. She has also been able to correlate to some extent the social condition of the family with the presence or absence of this growth failure. I myself have been able to guess children's family circumstances by observing how well they were in comparison with other children of the same age. She can do it much better. She has two groups—one socially depressed, and one socially better off—and has been able to show that growth-failure occurs much more in the one than in the other.

GOPALAN: I am not very happy about the use of the term 'pre-kwashiorkor'. I think it is difficult enough to define and agree on what really constitutes kwashiorkor. When we begin to speak of 'pre-kwashiorkor' I think we are apt to make confusion worse confounded, because, after all, what is it? The stoppage of growth or the hair changes? If you are going to call that 'pre-kwashiorkor', or 'potential kwashiorkor', I do not know where we really stand with regard to this in India. When I go to a rural community, if I find that nearly 100% of the children are to be diagnosed as pre-kwashiorkor, the term loses its meaning, because stunted growth and hair changes are so non-specific. I don't think we should equate them in any manner with the full-fledged syndrome of kwashiorkor.

SÉNÉCAL: I think that is true.

GOPALAN: There is already so much loose thinking about this syndrome and, shall I say, confusing terminology that I don't think we should add words like this. Probably there are many subclinical cases which are not full-fledged kwashiorkor, but I think that either we recognize kwashiorkor as such or we do not. There is no point in talking of pre-kwashiorkor, considering, as we do, that these signs which are being mentioned are so non-specific.

SCRIMSHAW: Perhaps we should be careful how we talk about it, but we certainly have to think of this syndrome as evolving gradually. Kwashiorkor is not something that suddenly appears clinically without previous changes, so it is useful to talk about it at the subclinical level.

HILL: But does it evolve gradually? I am thinking of families where you have only one case of kwashiorkor, and yet the background is the same for the whole family. Therefore, although there may be a substratum of deficiency, what precipitates the case of kwashiorkor in the single instance?

SCRIMSHAW: We feel, in Central America, that we have a very large number of children set up for kwashiorkor; then an infection or a heavy infection comes along and causes diarrhoea, so that the children are put on a special diet of sugar water or barley water or rice water. As a result of that they very rapidly evolve into clinical kwashiorkor.

GOPALAN: Yes, but are there not many children presenting those manifestations who never develop kwashiorkor? If so, the term 'pre-kwashiorkor' loses its meaning.

RAO: From the point of view of public health and prevention, the earlier signs and symptoms are very important. Prevention is going to be discussed tomorrow. At the moment our object in discussing certain signs and symptoms is to find out whether we can define the earlier signs with the present knowledge at our disposal, and to resolve the confusion about terminology.

RHODES: I feel that what Dr Aykroyd said about continuing protein deficiency in children is most important. After all, kwashiorkor is peculiar only to a limited age group. We think there are protein deficiency diseases other than kwashiorkor in children in Jamaica. Protein deficiency goes on throughout childhood, and even though a child may pass the kwashiorkor age without showing signs of kwashiorkor, the protein deficiency may, at any point, give rise to signs and symptoms of disease, particularly if an infection or a further drop in the already low diet add to the burden. The only early sign which we can see throughout infancy and childhood in these cases is low weight and retarded growth. Some of these children have enlarged livers, and some of them show biochemical abnormalities of a kind that are commonly found in people living on a low protein diet, such as a low serum albumin and a low pseudo-choline esterase.

CLEMENTS: I think that you and Dr Scrimshaw agree on the fact that there are a large number of children in tropical countries who show retarded growth, compared with the rate that is considered optimal in other countries, and that then some sort of a crisis precipitates the onset of kwashiorkor. I gather that is what you said, and that there is a good deal of agreement around the table.

SCRIMSHAW: Yes, but I think a further qualification is needed; apparently in some cases it develops almost explosively as a consequence of very severe precipitating circumstances, and at other times it develops very slowly and the children seem to drift gradually into it. This fact greatly reduces the precision with which one can define the time of onset.

DIARRHOEA AND STEATORRHOEA

SANTOS: In Brazil diarrhoea is often one of the presenting signs. In a series of eighty-two cases, fifty-eight had diarrhoea, which amounts to 77%. We think the diarrhoea particularly important, because it usually leads to the child being put on a restricted diet, as Dr Scrimshaw said, which aggravates the protein deficiency.

AYKROYD: Would I not be right in saying that that is a common finding everywhere in the world where kwashiorkor has been observed? I have never read any account of this disease under any name in which that point was not made.

SCRIMSHAW: There is also the difficulty of determining in a given case whether diarrhoea is the precipitating factor or a consequence of the disease.

RAO: Yes, the same holds for any clinically important symptom.

CLEMENTS: How do you determine whether diarrhoea is a precipitating cause or a result of the disease?

STUART: Most of our cases—about two-thirds—come up with diarrhoea as a presenting symptom, and we agree that some gastro-intestinal infection or infestation is a frequent cause of the nutritional breakdown that produces kwashiorkor.

CLEMENTS: You are implying, then, that it is a precipitating factor and not part of the disease?

STUART: Yes.

SCRIMSHAW: That doesn't really answer the question, because once the disease is established or once the children are on one of these rice and sugar-water diets, the diarrhoea does not stop until proper dietary treatment is instituted.

DEAN: Our children are very seldom brought to us because of diarrhoea. That seems to be quite different from your experience. When we go into the history with the mother, we nearly always find that at some time there has been some diarrhoea, but we are quite unconvinced that there is a close connexion between that and the mother's bringing the child to hospital.

On the other hand, if I go back to Dr Welbourn's experiences with children from her clinic, she has observed children who were not doing as well as they should and in whom an episode of diarrhoea began the downhill course which ended in their admission to hospital.

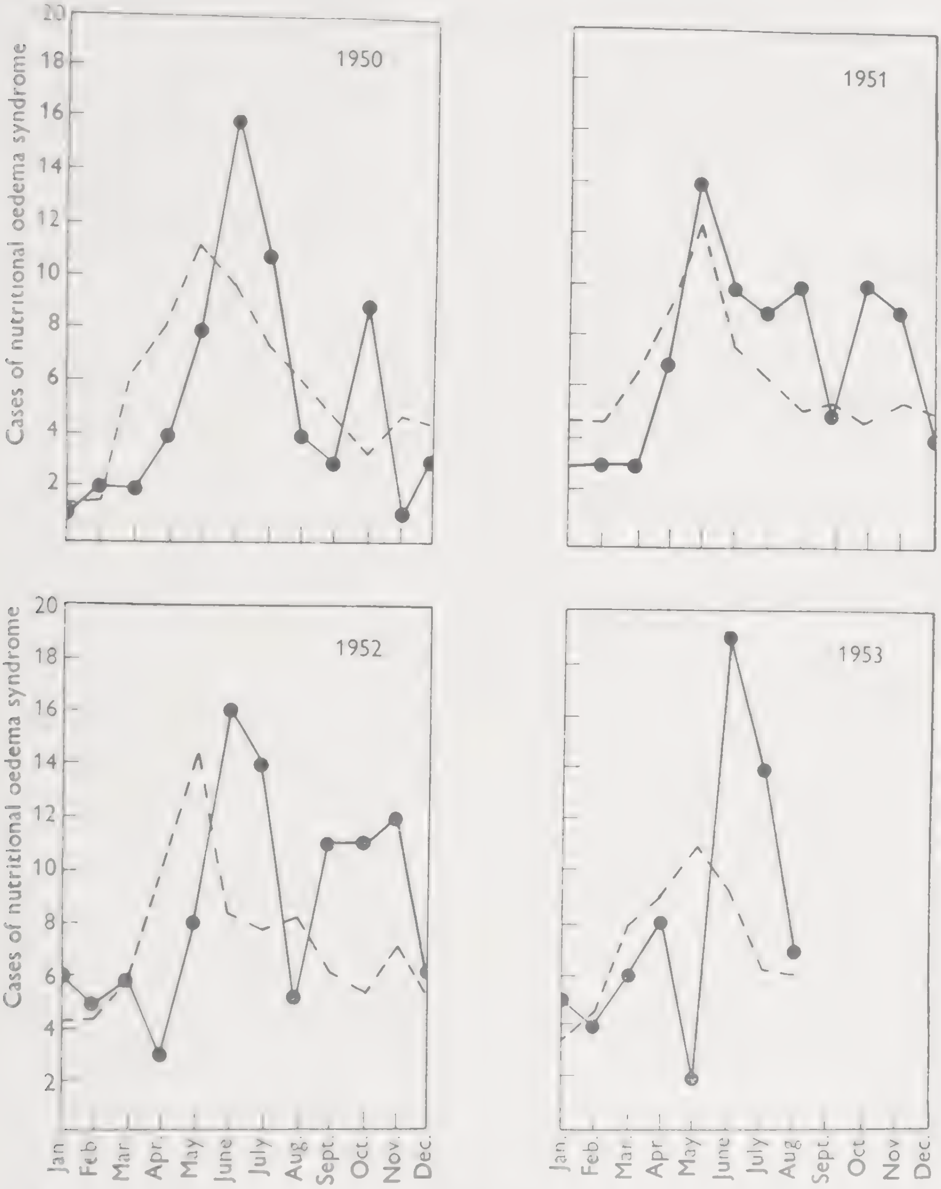
GOPALAN: May I show some figures on this question, just to illustrate the point that diarrhoea can be a precipitating factor, in addition to its being a feature of the disease itself?

In this chart (Text-fig. 18) I have attempted to indicate the incidence of kwashiorkor month by month for 4 years. Every year there has been a peak incidence in the months of May and June. That is striking, because the community from which these cases are drawn consists of plantation labourers, who do not depend on the land for their sustenance, so you cannot attribute this seasonal fluctuation to pre-harvest shortages. It is not a reflexion of the 'hungry months', because these labourers get a constant, fixed income throughout the year. Therefore I feel that the seasonal fluctuation, which occurs every year, is interesting.

I think the reason for it is this: the months of April and May constitute what one might call the 'fly season' in Coonoor. It is during that period that we also get the maximal incidence of infective diarrhoea, which I have plotted with the interrupted lines. You will notice that the peak incidence of infective diarrhoea immediately precedes the peak incidence of kwashiorkor. Of course, it is only circumstantial evidence from the epidemiological standpoint to suggest that diarrhoea has a precipitating effect.

In Malabar, on the west coast, there are two factors which operate. The months of May and June, as in Coonoor, constitute what we might call the 'diarrhoea months'. Those months are also the 'hungry months' there, being the pre-harvest period. That is why we get the most fulminant and the most numerous cases of kwashiorkor in Malabar. I think that there the food factor and the infective factor synchronize, but here in Coonoor there is evidently only one factor operating.

In addition to this, as Dr Scrimshaw has pointed out, we do find diarrhoea occurring as a feature of the disease, and in most of these cases we are not able to demonstrate any pathogenic organisms. These diarrhoeas respond very satisfactorily to skim milk.



Text-fig. 18. Monthly incidence of nutritional oedema syndrome (kwashiorkor) and of gastro-intestinal disturbance, Coonoor, India. ——, nutritional oedema syndrome; – – –, gastro-intestinal disorders.

Clements: But I am not convinced that diarrhoea is a feature of the disease, in the sense of being a consequence rather than a precipitating factor. What is the evidence for that conclusion?

Mackay: Do you get diarrhoea in rats on a protein-deficient diet?

Gyorgy: No.

Stuart: A pathogenic organism—*Salmonella*—was isolated in only 7% of our cases of diarrhoea.

Clements: The only evidence that we have so far is the point made by Dr Gopalan that the diarrhoea clears up on treatment simply with skim milk. Perhaps it is related to the atrophy of the pancreas and gut, and the failure of enzyme production that we discussed in the first two sessions.

Gopalan: In this connexion I might add that nearly 70% of cases of diarrhoea that we see in Coonoor have fat globules in the faeces. We see them even in cases which have been put on a skim milk regime, which supplies very little fat. We have been intrigued by this phenomenon, because we do not know where the fat actually comes from. These children continue to pass fat globules in spite of the fact that the diet does not supply any appreciable amount of fat.

Cruickshank: Have you actually estimated the percentage of fat?

Gopalan: No, we have not done fat balance studies.

Dean: There is no doubt about the steatorrhoea. We have measured it, and other people have measured it, and in looking through the literature I find some very interesting correlations. One of them is in Dr Van der Sar's data—a correlation between a high level of total fat in the blood and the amount of fat in the stools. That interested me very much, because it suggests that the fat in the stools might be secreted into the gut and come in that way from the blood. We have fed children on diets which contain no fat at all, and yet got a lot of fat in the stools. The diet on which children in our locality get kwashiorkor contains extremely little fat. The diarrhoea, I think, must be related to the steatorrhoea. The actual mechanism of it is difficult to elucidate. Professor Frazer suggested that it might be due to some abnormality of fat-splitting, and the production of more or less noxious fatty acids, but that is uncertain at the moment.

If you add milk fat to the diet of these children you immediately provoke an extremely severe diarrhoea. There seems no doubt that you can change the gastro-intestinal flora of these children very easily. One way of doing it is to add some milk fat; another way is to add excessive lactose, of the order of 60–80 g. The way of preventing it seems to be to add, instead of milk fat, soya fat, for which there is some justification, I think, on physiological grounds.

Clements: This whole field has been very well covered by the Dutch workers, hasn't it, working on coeliac disease?

Dean: But not on kwashiorkor.

Clements: I know, but how are we sure that the same mechanism does not operate with respect to the fat in the stools?

Gyorgy: According to the most recent concept, coeliac disease may be due to intolerance to gluten, perhaps through allergic reactions which prevent fat absorption through the lacteals. It has nothing to do with kwashiorkor.

Dean: We have just started some work on that, in which we have tried the effect of giving bread, which we would expect to provoke a coeliac-like reaction, and it has not done so.

Mackay: Is the steatorrhoea always associated with diarrhoea? If it is, it would rather suggest that the gut membrane was abnormal and that the fat was coming from the gut. But if you get fat in the stools without diarrhoea, the absence of diarrhoea suggests a more normal gut membrane.

Dean: I think there is no doubt that the gut membrane must be abnormal. At the same time, in these bad cases, the pancreatic enzymes are extremely low in amount.

Mackay: If you have no fat in the diet, you have to explain where it comes from.

Gyorgy: I am not happy about your statement that there is no fat in the diet. Skim milk contains fat.

Dean: But less than 1 %.

Gyorgy: You have a higher output than intake?

Dean: Yes.

Gyorgy: That, of course, is the important point.

Stuart: As far as ordinary clinical observation goes, in Jamaica we never see steatorrhoea in cases of kwashiorkor. I wonder whether it is universal or just happens in Uganda and in India.

Waterlow: I measured the faecal fat in a few cases here in Jamaica. The 24-hour output was not excessive, and the partition of fat and fatty acids was normal.

Clements: I do not think we have the data to answer Dr Stuart's question. Clearly there is need for more work on this aspect of the disease in different parts of the world.

If there are no more comments we might pass on to the next subject.

HEPATOMEGALY

Rao: The next sign I want to discuss is hepatomegaly. There has been some difference of opinion about this. We must consider whether there is characteristically an enlargement of the liver in cases of protein malnutrition, and if so, how big it is, and what is its consistency.

Waterlow: I mentioned yesterday, and I should like to emphasize again, that of the places I have been in, Jamaica seems to produce the biggest livers with the greatest frequency. I feel convinced that there is much variation in different parts of the world in this respect, so that it would be well worth while collecting evidence widely. As I said on the first day, I think that the size of the liver may be related to the operation of two factors working in opposite directions; it may be increased by excess of fat and perhaps of water, and decreased by loss of protein. Because changes in the size of the liver may possibly be interpreted in chemical terms, however rough the correlation may be, I feel that hepatomegaly is something which should receive a great deal of attention from all of us.

Van der Sar: In all the children with kwashiorkor that I have seen, I have considered enlargement of the liver. I found it not palpable in 3%; just palpable in 40%; palpable to two fingers below the costal margin in 33%; and three or more fingers' breadth below the costal margin in 23%.

Dean: In our children the liver is not very much enlarged below the costal margin. I think it is only palpable because the children are so small. I have heard Dr Waterlow so often on this question of the enlarged liver in Jamaica, and have therefore made it a point, wherever I have gone, to try to find similar examples. I should like to hear what Professor Sénécal has to say on this. Halfway between Professor Sénécal and myself, there is Dr de Meyer, working for I.R.S.A.C. in the Congo. When he first went there he found at once children with enormous livers, but he now tells me that these big livers are quite rare, and that most of the children do not have any enlargement of the liver.

There are two things which might be correlated. In Uganda we do not get ascites and we do not get enlarged livers. I will not go further than that, but I think it might be a fruitful ground for investigation in the future, if not for discussion at the moment.

Waterlow: Let me make it quite clear that I am not talking about the V.O.D. liver with obvious ascites. I am talking about the 'sugar baby', 'fatty liver disease', or kwashiorkor.

Dean: But some of those do have ascites, apparently.

Waterlow: Only very small amounts, if at all; not clinically detectable.

Scrimshaw: In Central America we do not often encounter either liver enlargement or ascites. I believe, in the draft of the report on kwashiorkor in Central America by Dr Autret and Dr Behar which was distributed at the recent Nutrition Conference in Caracas (46), the liver is not even mentioned, presumably because it is such an unimportant part of the syndrome in Central America!

Autret: No, because you had an incomplete draft! Moreover, at the time of our survey very little information was available on pathological examinations of the liver in kwashiorkor in Central America. The only published paper was that of Fallas Diaz & Nettleship (47). No puncture biopsies or post-mortem examinations were done in most of the places visited.

SCRIMSHAW: But you did not find hepatomegaly a prominent feature in your tour in Central America?

AUTRET: We did not find the great enlargement described in French West Africa, for example. There was some, but it was neither constant nor important.

WILLIAMS: On the Gold Coast a large palpable liver was the average condition of the average child.

CLEMENTS: Any child?

WILLIAMS: Yes, so much so that I thought the enlarged liver was a symptom of malaria, because that was almost universal. I can't say whether the cases of kwashiorkor had larger livers than the average child, but a great many cases started with an enlarged liver, and as the disease progressed, the size of the liver decreased. In those that came to post-mortem, the liver might be quite small but still contain a percentage of fat.

GOPALAN: Our experience in Coonoor is very much like Dean's. We find the liver enlarged in only about 20% of our cases of kwashiorkor.

PEÑA CHAVARRIA: In Costa Rica, in those cases that have no history at all of malaria, we do not see enlargement of the liver unless the kwashiorkor is very far advanced.

SANTOS: In Brazil enlargement of the liver is fairly prominent among the symptoms and signs we have been discussing. It is found in some 40% of our cases.

AYKROYD: Dr Waterlow, in your survey in Brazil in association with the Brazilian workers, you reported a rather low incidence of liver enlargement. Did you evolve any idea of the cause of this difference between Jamaica and Brazil?

WATERLOW: My impression was that the typical case of kwashiorkor in Brazil was thinner than its Jamaican counterpart. I think that the liver in these cases may be smaller because it contains less fat. This goes hand in hand with a smaller amount of subcutaneous fat and probably a smaller calorie intake, as judged by Dr Vergara's histories; that is to say, in Brazil we were seeing something nearer marasmic kwashiorkor than the type of case we get in Jamaica, that Platt called the 'sugar baby'. But that is only a guess. I myself was able to do only four biopsies, none of which showed maximal fatty change, and I was not able to see very much pathological material to support or refute that theory.

BURGESS: A paper that you quoted, Dr Waterlow, is of some interest, the work of Dr Gomez of Mexico (48). I think he states that the liver enlarged on treatment?

Waterlow: Yes. It is a peculiar phenomenon, which I think Dr Gyorgy knows more about.

Gyorgy: The syndrome of convalescence. In children with kwashiorkor the liver enlarged considerably during treatment, when the treatment was uncontrolled.

Clements: Are there any other examples of the association of hepatomegaly with other signs and symptoms that we have been discussing?

Waterlow: I was originally sent to the West Indies to investigate oedema. The first thing I noted was that every child I saw with oedema had a big liver, and then I went on to find that many children had big livers, who did not have oedema.

Dean: It is, perhaps, because of the lack of enlargement of the liver in Uganda that my own feeling about kwashiorkor has been directed towards trying to prove that it is a generalized condition in which the liver plays only a minor part. I should like to put it on record that I think the pathological discussion yesterday was perhaps concentrated too much on the liver and not enough on the possibility of the liver being only one of the organs affected and not even the chief organ. As Dr Clements has said, it is very accessible, and it might be that people have been a little influenced by that. There are some workers, like Davies, who suggest that the pancreas is a more consistently affected organ than the liver. That fits in with the observations which Dr Gyorgy says were originally made in 1891 in Germany.

Stuart: If I may disagree with Dr Dean, I think that all of us know kwashiorkor in our own area, and we must think of it as we see it in our own area. In Jamaica enlargement of the liver is one of the most obtrusive signs, and I think it is not unnatural that we should lay more emphasis on it here than he does in Uganda, where he doesn't see it.

Dean: It may not be the most important.

Bras: Since Dr Dean suggests that undue weight was put on the liver yesterday, I would like to say that the choice of the liver as the first organ to be discussed was influenced by the fact that it is the organ best studied. Further, I considered myself in very good company when I made that choice; I may refer to various reviews of kwashiorkor that have been made. Dr Davies, discussing the pathology of kwashiorkor (29), starts with the liver changes, and goes on to the pancreas; after that he discusses the other organs. It was precisely that sequence that was chosen by me.

I admit it is confusing that here in Jamaica we seem to have two different types of liver enlargement and liver pathology. One type, the fatty liver, is associated with kwashiorkor; the other occurs in somewhat older children, and is usually characterized by the histological changes of V.O.D. that I described yesterday. We think that both these types of hepatomegaly are related to malnutrition. As far as this second type goes, Dr Rhodes gave us the evidence yesterday. The importance of the topic lies in the principle introduced, that of the joint operation of two factors.

MENTAL CHANGES

Rao: We are now near the end of my list. The next symptom which I propose to discuss is lassitude and any other mental signs and symptoms which you may like to bring forward.

Clements: I saw a child in the ward yesterday, 15 months old, lying on its face, that might have been a case of pink disease. There was no doubt that that baby was suffering from lassitude and complete lack of interest in the world. That is considered to be one of the features of kwashiorkor, but I just wonder how much of that might be due to maternal deprivation. When children are at that age, up to 2 years, their interest is in people. Consider a child of that age who has been abandoned or left by its mother because she has gone to work; its apathy undoubtedly can be a sign of kwashiorkor, but I think it can also be due to the other conditions which accompany and cause the development of the disease.

Williams: Many of our cases were not parted from their mothers at all.

Clements: And they still had this lassitude, with that apathetic appearance?

Williams: Yes.

Dean: I agree.

Gyorgy: I have seen cases in Guatemala in a village where the children were very well taken care of by the parents.

Dean: Do you in Jamaica get a similar degree of lassitude in children who have not got kwashiorkor but who have got some other form of malnutrition?

McCulloch: Yes, in marasmus.

Stuart: I don't think we see as much lassitude as is described from other places. I think the marasmic type tends to show much more lassitude than the type that we call the 'sugar baby'.

Peña Chavarria: The psychological condition of the children in our severe cases is characteristic. They are indifferent to their surroundings and remain immobile for hours, with the eyes open but expressionless features, suggesting a less than human face. Often this is accompanied by a monotonous cry, without tears. All offers of food are rejected, and the least touch is resented. I also want to mention a sign that in our hospital I call the 'candy test'. On my rounds I usually give a piece of candy to every child; in the cases of kwashiorkor I would even put the candy near the mouth and they would not pay any attention to it. That is what I call the 'candy test'.

DIFFERENTIAL DIAGNOSIS

Clements: Before we end we might consider very briefly conditions which have to be differentiated from kwashiorkor, presenting some of the same symptoms and signs, but not due to uncomplicated protein deficiency.

Williams: The first condition is beri-beri. A child with acute cardiac beri-beri presents with oedema; typically it is relatively well nourished, but at the same time desperately ill. The treatment is injection of thiamine, first intracardiac and then intravenous. The immediate response to thiamine is an absolute diuretic deluge, quite different from any response you get with oedema due to other causes.

Another condition that has to be distinguished is worms. I remember a Chinese child who came into hospital from an ordinary Chinese diet. It was emaciated, with oedema of the extremities and a very well-marked oedema of the face, not only of the eyelids, but particularly of the cheeks. There was no anorexia or diarrhoea. The skin was dry, but it was not the typical picture. This child, on deworming, produced something like 200 ascarides, and immediately got well. This, I think is not kwashiorkor.

In the late stages the diagnosis is more difficult. Another case that I recall had been passing worms for a long time, according to the history given by the mother, who was unusually intelligent. When it got into hospital we could find no trace of worms. This child died. I think that very often, with ascarides, the rats leave the sinking ship; the effect of the worms is to kill the child, yet by the time it comes into hospital, if it is a late admission, there are no worms to be seen in the body at all. This particular child was emaciated, with a certain amount of generalized oedema, much oedema of the cheeks, and very marked depigmentation. Both parents were full-blooded Africans, but the child was quite pale in colour. The intestines were atrophic, and I think that the effect of the worms had been to destroy the power of absorption altogether. This type of case I did not call kwashiorkor.

There has been a good deal of discussion about weight loss and emaciation. I do not feel that this is of any value for differential diagnosis between kwashiorkor and marasmus, but merely indicates the *chronicity* of the process, whatever it may be. For instance, these children who have had worms for a long time are very emaciated. Another point I would like to make is that flabbiness and atonia of muscles and subcutaneous tissues is an early sign, though again not specific.

Clements: I would like to clarify one point. Did the Chinese child with worms and oedema—the second case you mentioned—have an enlarged liver?

WILLIAMS: The liver was not markedly enlarged.

CLEMENTS: Were there any skin changes?

WILLIAMS: Only a dry skin.

CLEMENTS: The only signs, then, were loss of weight, slightly depigmented hair, and marked oedema. When the worms only were removed, the condition improved?

WILLIAMS: Yes.

CLEMENTS: Dr Gopalan might want to say that that was a disturbance of protein metabolism; would that be right?

GOPALAN: I was going to suggest that cases of this kind (except, of course, cases of beri-beri) could have been diagnosed as kwashiorkor from those symptoms by other clinicians. I think it revolves around the question, what are the criteria? It is too late in the day to start discussing that, but if we accept stunted growth and oedema associated with hypoalbuminaemia as criteria, I do not see why cases such as the last two you mentioned, Dr Williams, should not be called kwashiorkor.

WILLIAMS: It all depends on how long the condition has gone on. What struck me in these cases was that sometimes it was so fulminating that there was no time for a defect in growth to appear, but if it was a more chronic condition, you might be able to detect the failure of growth, though not in every case. These children were seriously, but not acutely ill, and they did not develop the typical picture of kwashiorkor.

GOPALAN: In 80% of cases of kwashiorkor, or the condition we call kwashiorkor, we found very heavy roundworm infestation. It is not unusual to find a case where you give just a grain of santonin, and the child excretes something like 120 roundworms; so if all cases complicated with roundworm infestation are to be excluded from the category of kwashiorkor—

WILLIAMS: I'm sorry; I wouldn't exclude them at all. My point is that the child was heavily infested and showed plenty of signs of infestation, but did not have kwashiorkor.

CLEMENTS: You could probably help us, Dr Williams, by saying why it did not have kwashiorkor.

WILLIAMS: I don't think it had the typical skin changes, it had no anorexia, it had a voracious appetite, its mental outlook was depressed but it did not have acute melancholia—the active melancholia which the kwashiorkor children have.

CLEMENTS: I think you leave some of us unimpressed that it wasn't kwashiorkor.

GOPALAN: I think there can be no difference of opinion with regard to the child you described as beri-beri. I am prepared to make a clear-cut distinction only between that one condition among those you have mentioned, and kwashiorkor. I am not prepared to accept anything like hard-and-fast definitions for this syndrome. Considering that these cases can present so many variations determined by regional factors, the only two criteria which I accept are stunted growth and oedema associated with hypo-albuminaemia. I know that there is nothing specific about these criteria, but, as a working rule, I think they should be satisfactory, for they represent the commonest and most invariable features of kwashiorkor as described from different parts of the world.

CLEMENTS: I think this is a very important stage which we have reached, because it means that some of us have come with fairly definite ideas of a limited syndrome, anything outside which is not kwashiorkor, whereas there are others who are prepared to spread the net very widely. One of the things we ought to aim at doing is to reconcile these two points of view, if they are two points of view.

RAO: They are, sir.

MACKAY: Did these children have a normal protein intake?

WILLIAMS: I couldn't say accurately. It was low, but I couldn't give figures.

MACKAY: From the body's point of view, a protein deficiency may be either dietary or it may be due to competitive action of some parasite. In the end, you get protein deficiency in either case.*

WILLIAMS: Yes, that is true.

MACKAY: Is there then any reason why you shouldn't get kwashiorkor indirectly?

WILLIAMS: I quite agree that it might be secondary to something else.

TREATMENT

RAO: I shall now go on to some aspects of treatment. I suggest that we confine our attention to principles in the treatment of children with protein malnutrition, because all the clinicians will no doubt agree that in the wards we treat not the disease but the child. Therefore the treatment varies from place to place and, perhaps, from clinician to clinician. For instance there has been some discussion about giving blood transfusions. That is a point which it is necessary for us to discuss. Another important aspect is the question of giving vegetable proteins, and that is a subject in which I am particularly interested, coming, as I do, from a region where milk is in very short supply. We must therefore consider the principles of treatment which are representative of the different areas from which we come.

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* Bray (20) has done nitrogen balances on children with worms (ascaris and ankylostoma) and found no evidence of any competitive utilisation of nitrogen by the parasite at the expense of the host. (J. Waterlow.)

DEAN: When I went to Uganda the first thing I found was that these children were short of protein, and I decided that the way to treat a child who had been short of protein for a long time was to give it a great deal of protein. You have, possibly, read some of the work which we have published on this subject, and I need not go into details.

It seemed obvious that we must give the protein in the most soluble form, and so, after a few trials and errors, we began to give calcium caseinate in the preparation made by Glaxo called Casilan; with this we found we could get a great deal of protein into the children and it rapidly improved their clinical condition. That was a very expensive treatment, and I couldn't understand why we should not give the same amount of protein in the form of dried skim milk. I then discovered that when I gave dried skim milk instead, enough to provide the same amount of protein, I got diarrhoea, which I was able to track down to the lactose in the milk.

The treatment which we have evolved, and which we think is the most effective, is to give very large amounts of milk protein, mostly from Casilan, and not more than the same amount of lactose. I think that probably it is possible to cure almost any of our cases of kwashiorkor by giving 50 g. of protein in this mixed form and 50 g. of lactose, provided we give at the same time some sweet banana, which, we find, has a very useful effect in stopping any tendency to diarrhoea. I think it probably slows down the passage of the rest of the food through the gut and gives the gut a chance to absorb; since the mucosa is very badly damaged, more time than usual is needed for absorption.

That work was preliminary. My real reason for going to Uganda was to try to use plant proteins instead of animal proteins, and as soon as we had established to our satisfaction a reasonable method of treatment, we turned over to the substitution of plant proteins for animal proteins. For the first experiments I used soya. I thought I would have to use defatted soya, but, hoping to start in the simplest possible way, I used the soya without defatting it, and found to my surprise that the soya fat was extremely well tolerated.

We now have a treatment in which we give 50 g. of soya protein. The preparation of the soya is a kind of heat treatment which destroys the inhibitor and makes the soya palatable, and I think it probably makes it easy to digest. We put it with sweet banana through a Waring blender, making a kind of cream which the children seem to like and will take very easily. When I have done that kind of feeding I have always added a multivitamin preparation which provides, amongst other things, about 20 μg. of vitamin B_{12}. I still regard this work as in its first stages and I cannot tell you whether any parts of the multivitamin preparation are essential. That is another problem which has to be faced later.

The results of this treatment with plant proteins are similar to those with animal protein, except that I have had the impression that the speed of recovery is not so rapid. We have also found some rather interesting variations in the way in which the serum proteins appear to be regenerated. It seems that regeneration is slower on the plant protein diet.

We have followed all these cases with the same serial biochemical tests that we established at the beginning for our first treatments, and we are hoping that when we have improved the method of giving the soya, we shall find that the results are not greatly different from those we get with the best of our animal protein diets.

Gyorgy: Dr Dean, why did you give extra lactose to your cases?

Dean: I didn't want to. It was already in the dried milk. I should have explained that we gave a mixture of dried skim milk and calcium caseinate, which provided so much protein, and the same amount of lactose.

Gyorgy: Then you didn't give protein and lactose; you gave protein and skim milk; therefore, protein-enriched skim milk.

Dean: Yes, that's right.

Gyorgy: That is important, because then you still gave something which was in the skim milk, if there is something in skim milk.

Dean: Yes. We have also done experiments in which we did not give skim milk, but gave other sugars.

Gyorgy: But you said they were not as good?

Dean: No, they had the same effect as the lactose of the milk.

Scrimshaw: Perhaps it is pertinent to mention that Gomez (28), when he gave mixtures of either cow's milk or soya milk to undernourished children during their first year, observed equally beneficial results in everything that he measured except a slower increase in serum proteins.

Dean: Yes. At the moment we think that is probably due to our inefficiency in giving the protein. We haven't yet got a preparation which is nearly so easily assimilable, I believe, as the best of our milk protein diets.

Waterlow: How about the enzyme proteins in the serum?

Dean: They follow very much the same pattern of recovery with the two treatments. It is the serum albumin which does not seem to regenerate quickly. We get the same kind of rise in serum globulin which has been noted by many people. We start with a very high serum globulin in our cases, and I notice that in your cases the serum globulin often starts low and rises with treatment.

Bras: What influenced your decision to use soya, and have you considered using more than one plant protein? I remember in the East Indies, in early studies on nutrition, Professor van Veen discovered that it was much easier to produce an adequate supplement to replace animal protein, by mixing soya with another legume which is grown out in the East (*Phaseolus radiatus*), plus rice, which is the usual staple.

Dean: I myself worked for some years on this question of the supplementation of plant proteins, and surprised myself by being content with the mixture of plant proteins which I found in soya and banana. I did, in my first experiments, make a mixture of maize and banana and soya which I found was not so well tolerated. The maize in the form that we have it is not so good for these children. They cannot assimilate it well. Soya is the plant on which I have done the most work and which is best known, but our programme only begins with soya. Soya was available locally, which is to me a fundamental principle when you are trying to establish preventive measures. Maize was also available. That is why I used it and not wheat flour, which has to be imported from Kenya. Banana was also locally available. But you will, of course, not have missed the point that when I was giving banana and soya, I was, in fact, making a mixture of amino acids, although only a small part of the protein came from the banana.

McCulloch: But isn't it a fact that the proteins of soya and peanut are complete and biologically as good as wheat proteins? Aren't they the only two proteins which are in that range?

Waterlow: Peanut protein is rather low in methionine (31).

Gopalan: I think the main point to remember when attempting to evolve a line of treatment, is that kwashiorkor is a condition which occurs very often in rural communities, where facilities for hospitalization or for elaborate treatment often do not exist. That is why I do not feel very enthusiastic about resorting to blood transfusion, as advocated by some clinicians. The standard treatment which we have adopted for our own cases is to feed 6 ounces of skim milk powder, which is equal to 48 ounces of reconstituted milk, and 8 ounces of bread. We usually make the skim milk powder into a thick paste. On this regime we find the results are quite satisfactory. The oedema clears in about 3–4 weeks.

We have never adopted plasma transfusion as a method of treatment. In a series of 114 cases which we treated with just skim milk alone, our mortality was 7·9%. In a series of 300 cases which Professor Achar treated, resorting to plasma transfusion wherever he felt it was indicated, the mortality was 11%. I know it is wrong to compare the results of two series of cases dealt with by two different investigators in two different places, but I think these figures show that there is no great advantage to be gained from plasma transfusion. What is necessary is a simple line of treatment.

Recently we endeavoured to follow Dr Dean's example, and tried to treat some cases with a preparation containing 250 g. of Bengal gram, 70 g. of jaggery and 100 g. of peeled dried bananas, which we mixed into a porridgy consistency in an autoclave for 15 minutes at 20 lb. pressure. We have treated only twenty-five cases of kwashiorkor on this regime, and perhaps it is wrong to attempt any generalization with such meagre material, but with the limited experience we have had I can say that while the results are perhaps not quite as satisfactory as those which we have achieved with skim milk, all these twenty-five cases recovered without any complications. As a working treatment which can be carried out in a rural community and poor population, it may be found quite satisfactory.

The doubt that I have had with regard to this Bengal gram regime is this, that in our cases we find there is also a great deal of calcium deficiency, as shown by dietary surveys, and I don't think that we can put much calcium into this regime.

Dean: Why not?

Gopalan: It doesn't supply calcium as it stands now. We have to look for some other source of calcium. In the case of the skim milk regime, of course, the calcium is provided. That is an important difference.

Dean: I think that you always have to supply an artificial source of calcium. I think it is true to say that no plant source of calcium anywhere nearly matches skim milk or even unskimmed milk, in calcium content.

McCulloch: Sesame seed is eaten all the time by the tribes along the Niger River as a common source of calcium. In America, because of its high protein and high mineral content, it is being used for cattle and stock feed.

Clements: Have we any figures on the actual consumption of this by human beings?

McCulloch: I have not got them here. But another point which bears out what Dr Dean said is that in my time in Nigeria many tribes had an absolute taboo as far as milk is concerned, so we could not give it in hospital and had to devise a milk substitute of protein made from peanut, i.e. the peanut mass after the oil had been boiled out. We mixed it with ripe bananas, and had very good results with it in our children's wards. We diluted it down afterwards to make a drink for them, and certainly it was a good milk substitute for us in those days when we didn't know enough to trace the minutiae that were missing. Incidentally, I recall some work from Australia, many years ago, on the diuretic effect of pineapple juice; I think there is no doubt that pineapple juice instead of water, in children with ascites, has a very diuretic effect.

Burgess: I would like to ask Dr Gopalan a question. Dr Dean made the point of adding B vitamins, including vitamin B_{12}, to his diet. You didn't do that?

Gopalan: No.

Burgess: I think that Dr Dean regarded that as rather important.

Mackay: Have you a controlled study, Dr Dean, of these vitamin supplements?

Dean: No. I haven't had a chance to do that so far, and I don't know whether the B_{12} is the only thing that is required.

Clements: Are you sure that it is required?

Dean: No, because I have only done rat experiments. All these diets and additions to them are controlled by rat experiments, and this diet did work so much better when the supplements of the complete vitamin mixture were added that I decided, empirically if you like, to add it to the diet of the children.

Autret: Was this diet of soya and banana used in very severe cases?

Dean: Yes. At first it was not used in the very severe cases, but later on we began using it in children who were very much under weight, who had oedema and severe skin lesions—that is, children in an advanced stage of kwashiorkor, who, from our experience of similar cases, would certainly have died. As I say, this work is only at its beginning. We have done no more than establish that the treatment appears to have great possibilities.

I should very much like to have the views of the meeting on what the direction of experimental treatment should be in the future. It is quite obvious that we have to fractionate the protein we are giving by which we obtain good results, and find out, if we can, what it is that gives the good effects. But, as you know, a number of other treatments, such as choline, methionine, ventriculin, vitamin B_{12}, androsterone and other things have been tried for various reasons. I wonder if anybody has any idea of the direction in which our experimental treatment should proceed?

Waterlow: I think the first point to be tackled is how to assess the results of treatment, if possible over a short period of time, such as a week, so that you can compare one treatment with another in the same case.

Dean: It is just for that reason that we embarked on all the biochemical work I mentioned the other day.

Waterlow: Have you determined any criteria?

Dean: At least we have detected some slight difference in the two treatments I have already mentioned, and I think that if we go further along the same lines, we may be able to find more criteria.

Waterlow: I was disappointed in your reaction to my suggestion of nitrogen balance measurements, because it seems to me that the best treatment should be the one which produces the biggest nitrogen retention.

GYORGY: I don't think so. It has been tried in post-alcoholic cirrhosis, which I think we would all agree is based on long-standing malnutrition. Testosterone should increase protein retention; therefore it was obvious to recommend a combination of a high protein diet and testosterone. In general, the effect of testosterone, although it increases protein retention, is very disappointing in the treatment of alcoholic cirrhosis.

WATERLOW: Yes, but aren't you speaking now about effects on a single condition, cirrhosis of the liver, and not on the body as a whole? When we are treating the child with kwashiorkor we are not, as in the case of cirrhosis, treating mainly the liver; we are treating the patient as a whole.

GYORGY: You have a good point there, and I admit it would be logical to try testosterone in conditions of protein-depletion.

WATERLOW: Dr Raoult(20) presented some results of treatment with testosterone at the Gambia conference last year.

GYORGY: But I would again come back to my previous observation, that a balance study *per se* will not give us even the answer to your own question, in what organs the protein retention occurs.

WATERLOW: But that is a subsidiary question. I entirely agree that nitrogen balance or retention does not give the whole story. But I am puzzled, for instance, by reports on the bad results of treatment with protein hydrolysates, because, without balances, one has no idea of how much is retained. Moreover, I want to know what is happening during what I call the stationary phase.

DEAN: I feel that I have been rather unjust to Dr Waterlow about his suggestion of nitrogen balances; the reason that I originally said, in the first session, that I didn't think much of them was that I could foresee theoretical objections. But I have actually done some balances, and they showed that in the acute stage of severe kwashiorkor we have an absorption of about 72% of the nitrogen, and after 25 days' treatment the absorption goes up to 79%, which is a very satisfactory answer.

I would have gone further in saying that that was an excellent diagnostic method except that I got similar retentions of nitrogen in children in very different clinical states. I wasn't happy about the correlation between clinical condition and the results of my balance tests.

WATERLOW: But I wasn't thinking of this as a diagnostic test, but as an assessment of the success of treatment. For that purpose the most important thing is nitrogen retention, not absorption.

DEAN: The retention in my cases fell with treatment from 40 to 10%, showing that the treatment had reduced the body's deficit of nitrogen. I think such balances are probably useful for following a single child, but, as you know, they must be done for an absolute minimum of 4 days. It is an exacting procedure, and we wanted something simpler. There was one thing, though, which did come out of those experiments, and that is, that the ratio of urinary to faecal nitrogen changed dramatically during treatment. This is what you would expect, as normally there is much more nitrogen excreted in the urine and much less in the faeces, but in the acute stage of the disease it was the other way round. I want to go further with that, and I look forward to presenting some better results.

Clements: Are there any more comments on treatment?

Gopalan: I think there are some clinicians here who believe in blood transfusion. I should like to hear their views and their justification for the step.

Waterlow: In serious cases, when anorexia and vomiting prevent us from giving food by any other route, they must be used. I admit that I have not been very pleased with the results, but then these are the worst cases. What we have done has not been controlled.

Stuart: The children to whom we give blood transfusions are in a state of collapse and shock, and our feeling is that blood transfusion here would be as beneficial as it is in the treatment of the same condition in the adult.

Waterlow: We have a particular problem of treatment—that is, the child who vomits almost everything, even if you give it by gavage, and who has a combination of dehydration at one end of the body and oedema at the other. We do not like to give these patients subcutaneous fluids, as is usual for dehydration and vomiting. The obvious and only thing I can think of under such conditions is plasma. I would be very glad to know how others get round this problem.

Gopalan: There is no question that where you find the shock syndrome, plasma is definitely indicated. But in my experience it has not been usual to find cases which are vomiting so incessantly that plasma should really be used. I have never come across cases in which I found it impossible to give food by mouth.

Waterlow: Some of our babies become dehydrated from vomiting. I think this is an indication for plasma, if, as often happens, there is also hypoproteinaemia.

Clements: That seems logical. If there are no further comments on parenteral therapy I should like to return to Dr Dean's point of how to compare the success or otherwise of different dietary regimes.

Hill: At an earlier session some evidence was given that if you protect the mother you might avert the onset of kwashiorkor. Was that based on animal experiments?

Dean: Yes. I was arguing from experiments in which a short period of high protein therapy or of vitamin B_{12} or methionine added to an insufficient diet, appeared to protect the animal from the development of fatty liver. I did not want to draw the analogy which was drawn for me.

Hill: I wonder if we could have any figures for the long-term effects of treatment? You treat a patient successfully for kwashiorkor, and return it to its old environment. Does that child come back, or is he cured?

Sénécal: Those patients come back.

Van der Sar: They don't come back.

Peña Chavarria: In our experience they do come back. You can see this from the white bands in the hair in the pictures that I showed a little while ago.

Clements: Do all the others say 'Yes'?

Dean: No, I have never had one come back after having received what I consider a complete course of treatment.

Gopalan: Do I understand you to say, Dr Dean, that a case of kwashiorkor, once it has received the full course of treatment, has never come back to you? I have several times seen cases of kwashiorkor go home after treatment and within 3–4 months return in exactly the same condition.

Clements: What is a complete course of treatment, Dr Dean?

Dean: I hope to tell you that tomorrow.

Clements: There is a very important point here, namely, what are the criteria of adequate treatment? Why is it that in some parts of the world children apparently return with the disease several times? Is it because treatment in those places is ineffective, whereas in other places it is more satisfactory? We have heard a series of recipes or menus; how effective are these forms of treatment? For how long should they be continued, and at what stage should the child be transferred to a normal diet, either a good hospital diet, or the diet of the village? Finally, what is the prognosis in these cases? All these are questions which we should consider.

Williams: I should like to emphasize that a thing of great importance is to take the mother into hospital with the child. We have made that a very large feature of our treatment—maternal attention to children of that age. In the Gold Coast the mother's attention to the child slackens off when she becomes pregnant with the next one, and unless you instruct the mother to look after the child after it goes out, I think it is a sheer waste of time to bring it into hospital.

Another thing I should like to emphasize is the importance of warmth. We were talking about that in the first session. I found the radiant heat cradle extremely useful.

A third important point is to use local foods as far as possible; if you have to introduce any imported or unaccustomed food, try to introduce it with the local food and teach the mother exactly how it should be prepared.

Very often the local food is there and available, but the mother has to be taught that this is the way to feed the child and not the way she has done before. I think many of my recurrences were due to the fact that I had not taken sufficient trouble over teaching the mother what to give the child after discharge from hospital.

Clements: What is the treament you are using? For how long do you carry it on?

Williams: Milk was the main thing, but sometimes eggs for the older children. If milk was completely unobtainable in the village, we would teach them to take a fresh egg and beat it into the banana, or into the maize meal. It is too long to go into now, because we have various tribal patterns and we have to try to introduce the food in different ways.

Clements: How long did you carry on this kind of treatment?

Williams: It depended on the severity of the case. If they had reached the marasmic stage, when they were not absorbing their food, it took a very long time.

Vergara: I would like to mention a recommendation made by the Latin American Nutrition Conference held last month in Caracas, that the child should not be kept for too long a time in the hospital.

Clements: What is too long a time?

Vergara: After the acute phase of the disease is over, when the child can walk, I would say that he is in a condition to leave the hospital. Then we can take him, for instance, to a vacation colony where he can continue to have a good diet. There is a psychological problem implied, making it desirable that the child should be taken out of the hospital environment as soon as possible. Furthermore, there are economic reasons, since it is expensive to occupy a bed in hospital when treatment can be continued elsewhere.

Clements: Dr Williams has made the point about the need for preventing maternal deprivation. Did this recommendation take that into account, and include the mother's going into the colony?

Vergara: No, not that point particularly.

Clements: But then you are setting up a foundling institution in which you are going to put children under the age of three, when their great need is for maternal care?

Burgess: That is true. But the point made in the recommendation was that the child should return to conditions resembling his own home rather than those which exist under the somewhat rigid hospital discipline.

Clements: I want to ask Dr Dean at this stage if he will please tell us what are his criteria for satisfactory treatment, and why is it that he does not get any return cases.

Dean: The great majority of our children have been treated for a period of 4 weeks, since our high protein diet has been established. The way in which we followed the effects of the diet was, first of all, by the clinical condition, and, secondly by various chemical criteria which I shall mention in a moment. We began with the therapeutic trial of substances which were locally used. I think I mentioned that at one time we were using mixtures of maize and soya, but gave them up because we had some trouble from the maize. We found that if we put maize into a diet too quickly the child reacted by diarrhoea and started to go downhill. We were able to devise therapeutic tests which showed whether the digestive apparatus of the child was functioning normally.

McCulloch: Did you prove it was the maize or the coarseness of the grinding of it? I have had trouble that way.

Dean: I am almost certain it was the coarseness. For most of this work I took out material about which I could be certain, material made in England, where I could know everything about the details of preparation. This is important. The local maize is full of grit. But I did not get the expected good results even when I took the best maize available.

McCulloch: I see. Thank you.

Dean: Anyway, I followed that plan for the first few months of my work, and then I realized that on discharge the child had to go back to a diet over which I had not control, and I had to decide whether I would arrange for transition to that poor diet or whether I would try to give the child the utmost benefit of hospital treatment. I was at that time, perhaps, too much influenced by the results of my animal experiments, which had suggested to me that a short period of high protein therapy might be protective and might have value over a longer period of time than I had at first expected. So what we have done since that time is to continue, throughout this month of treatment, an extremely high protein diet, and we have taken no notice at all of the fact that the child has to go back to a different diet.

We have also found that when we do introduce other foods into the child's diet towards the end of the month, it takes them extremely well. In the recovery phase it can be expected to take anything, just like a normal child.

The criteria that we use for treatment are not only the absence of a bad result when we offer something we know might be noxious, but also a series of biochemical tests, which Dr Schwartz and I published in the *British Journal of Nutrition* early this year, and which I have already mentioned [illegible] Briefly, what we find is a rise in the total serum proteins, a rise in the total cholesterol, a fall in the ratio of free to total cholesterol, a rise in the serum amylase and the serum esterase (that is the non-specific esterase that I have already mentioned), and a rise also in the alkaline phosphatase. All these things go parallel with rises in the duodenal enzymes. I mentioned that alkaline phosphatase is a peculiar enzyme, and that by our method I think we were estimating several alkaline phosphatases, one of which probably is of pancreatic origin and one of hepatic origin, and that the non-specific esterase may also have a dual or possibly a triple origin. But I am very much interested in that kind of test, because if we could establish an estimation which showed what was going on simultaneously in two or three of the organs we know to be profoundly affected, it might be possible, in a one-shot estimation, to get some idea of the progress of the child under a specific therapy.

I would like to throw out to the meeting this idea that it would be extremely valuable if we could get some estimation that shows what is going on in several organs.

The nitrogen balance, of course, does that, but it is difficult to do, especially in girls, and very time-consuming; we want something simpler. But there is no doubt that Dr Waterlow is quite right; it shows the sum of a great many processes.

WATERLOW: I think of it as a base-line for checking the validity of some simpler biochemical procedure. That, I think, is its main practical value.

DEAN: Yes, I agree. We have done some balances, and tried to fit them with all these other tests. If we did get any test which we thought might be valuable, we would have to go back and check it against nitrogen balances and also against any other test that we could devise.

WATERLOW: How much average weight gain do you expect to get with your treatment?

DEAN: Weight is a very important objective measurement, but, as was discussed in the first session, it is complex, being made up of so many factors. I must emphasize that my interest in this particular phase of the work was not so much in following the cure of kwashiorkor in any circumstances, but in following it in relation to different diets. My job is to try to make use of plant protein diets, and it was necessary for me to have objective criteria by which I could compare the effects of different regimes.

On the question of relapses, I should have said that, as far as I can remember at the moment, I have not had an opportunity of seeing any child, except one, more than 6 months after discharge from hospital. I have had one other child in hospital for one year, but I don't think that was a very severe case. The test would be to take the very bad case and follow it for a year or two.

As you probably know, we are building a new Medical Research Council Group laboratory in Kampala, with its own ward, and one of the things

I have promised myself to do is to take in some very bad cases and to keep them as long as possible, to get some idea of what the prognosis might be. It seems to me that unless we have some controlled observations over a long period we shall all be talking about things that we really don't know.

The lack of relapses was pointed out to me originally by Dr Trowell, who has infinitely more experience of kwashiorkor than I have. He was struck by the fact that although there were opportunities for mothers to come back to hospital with their children, they did not often do so. He would, however, be the first to admit that he was rather uncertain about the results of his treatment; in particular he was not always able to prevent diarrhoea, which we think we have more or less overcome.

Altmann, in South Africa, was one of the people who got good results lasting up to a year, and some other workers in South Africa have reported similarly. I don't think that these relapses are universal. I know that our follow-ups are bad, but Altmann and Brock between them have seen about forty cases whom they have been able to follow for a year or two, and although the signs in the liver may not have cleared, the clinical condition of the children appeared to be quite satisfactory.

CLEMENTS: Would anyone here who has seen recurrences, indicate in what way their treatment and handling of this type of case differ from Dr Dean's, so that we can get some comparisons?

GOPALAN: I think there is one factor which we must take into consideration in assessing these divergent reports about relapses. If you are working in a place where there are abundant hospital facilities, you may not be in a position to see if a case relapses, because it may go to another hospital. But, in a place like Coonoor, we have only one hospital and every case that relapses or that is remotely related to malnutrition must be referred to us. In our series I would say that at least 10% of our cases come back with relapses, and half of these come back on two or three occasions over a period of three years. I am not prepared to say whether relapses are more common in any particular type of case or with any particular type of treatment.

It seems to me that the diet which Dr Dean is giving is very much richer in calories and protein than it need be, though I may be wrong about that. In our own cases, which, I think, are certainly not milder or less advanced than Dr Dean's, we get very satisfactory results with, for example, a diet supplying 65 g. of protein and about 1000–1200 cal. for a 2-year-old child. Actually, when we start treatment, we don't give even that much. We give 2 ounces of skim milk powder, which would be about 33 g. of protein, and we gradually work it up to the maximum amount, that is, 65 g., in the course of about a week. We do that because, in our adult cases, we have been able to confirm the experience reported in other countries, for instance by Dr Keys, that too enthusiastic and too vigorous oral feeding, in an attempt to rehabilitate the patients quickly by giving them excess of calories and protein, may be actually harmful; so we don't believe it is necessary to give such high calorie and such high protein diets as Dr Dean is giving. At any rate, I can say that our results are quite satisfactory. I don't think there is any reason, as far as our material goes, for increasing the protein content.

The average duration of treatment in our series is about 3 weeks. After that we discharge the patient from hospital and allow him to go back to his home diet, but we ask him to come to our out-patient department to receive the same treatment, but only half the amount this time, for another 3 weeks. We know that this is not entirely satisfactory, but, after all, the control of the disease is not a hospital problem. That is why we are now trying to devise a line of treatment which would make the transition from the hospital treatment to the home treatment, as one might call it, less abrupt. That is why we are devising this Bengal gram regime.

We have done some work on the essential amino-acid composition of Bengal gram, and we think it is such as to supplement or to offset the defects in the poor rice diet; the great advantage of this Bengal gram regime, as we see it, is that it costs about a third as much as the skim milk regime. Perhaps an answer to this problem, considering that we have to deal with such poor communities, is to popularize the use of these pulses by the children when they get back home from hospital. That is a better method to prevent relapses, because although skim milk is the ideal treatment, I don't think that our patients will be in a position to afford it for a very long time to come.

PEÑA CHAVARRIA: Our general scheme of treatment is like that which has been mentioned, but our rate of readmission to hospital is higher than Dr Dean's.

CLEMENTS: Is your treatment similar to his?

PEÑA CHAVARRIA: Yes, it is much the same inside the hospital, but in my view recurrence does not depend on the previous treatment in hospital. It has to do with the economic situation in the homes. It is a peculiar thing, that the geographic distribution of our cases corresponds closely to the coffee-producing regions, and the incidence follows the coffee price, in such a way that when coffee is up, the number of cases that go to hospital are smaller. I have also noticed that, because of the distribution by U.N.I.C.E.F. in the last three years of powdered milk in the homes and particularly in the schools, the number of cases has diminished.

VERGARA: May I have some figures on the average stay of patients in hospital?

Peña Chavarria: It is at least 6–8 weeks.

Santos: We support substantially what Dr Peña Chavarria has said. The same thing is true in our country.

Hill: I should like to emphasize one point that Dr Gopalan mentioned, about increasing the diet gradually in hospital. When I was in Baghdad I was shown a series of cases not unlike those described here by Dr Rhodes. The patients looked not too badly nourished, and had much ascites, but with a fatty liver. They treated these cases very successfully with proprietary milk preparations and also by blood transfusion; there was no difference between the results with blood transfusion and with the milk-diet. One point they stressed very much was that if they had a very ill patient, it was no good putting him straight on to full-strength preparations of milk, but they had to nurse him carefully and make the transition gradually—quarter strength, half strength and full strength—as, I suppose, is well known to the fundamentalists, because if you give too much protein at one time to a body that is already suffering from protein malnutrition, the body just can't metabolize it.

Clements: Have you any experience from Baghdad on return cases?

Hill: Nothing definite. I got the impression that once they had been in hospital and had been treated for some weeks, then they didn't return. But, after all, they probably disappeared into the desert.

McCulloch: I think on this question of relapse the time factor is of enormous importance. The longer the child is under treatment and the better the recovery, the more impressed the parents are with what the dietary regime can do for the child. That child is also getting older, and as it gets older, it begins to experiment with more foods. That is why I think relapses are not as prevalent as one would expect. We are dealing with a deficiency disease, and one can expect the bad dietary conditions more or less to continue when the child goes back to its home environment, except for the age factor. The parents begin to experiment by giving it different foods—in fact, a little of everything that they eat. Here in Jamaica, as soon as the child begins to take what its parents have, it gets salted fish, salted meats, and so on.

Dean: I feel that some confusion may have been introduced by a reference that Dr Gopalan made to the work of Ancel Keys—that is, to the fact that if you give too large a calorie intake you are liable to get trouble. Keys was dealing with an experimental group in whom he produced hunger oedema, and his work was really the counterpart of the work that we did in Germany, where we observed the same condition produced by natural means, if you can call it that.

One of the things that Dr Widdowson did in Germany was to take a group of nineteen men suffering from hunger oedema into hospital and give them an unlimited diet for a period of 9 weeks (33). Over that period the average intake of calories per man was 6000 per day, and I know that one man took 9000 calories on several days. But the remarkable thing about those people was that although they had these colossal intakes, rich in fat as well as in protein and carbohydrate, not one of them showed any signs of intolerance except for transient episodes in which they possibly missed half a meal. There was nothing like the kind of upset which is normally associated with the giving of enormous quantities of food to starved prisoners of war.

Clements: This is a bit off the track.

Dean: Yes, but Dr Gopalan raised this in connexion with his work on the re-feeding of kwashiorkor. What he is talking about and bringing in as evidence is evidence from hunger oedema.

Gopalan: My point, Dr Dean, is this: Have you any concrete evidence to show that by giving this high calorie and very high protein diet you are getting better results than other workers are achieving or than you yourself can achieve by giving a diet that supplies 50 g. of protein for a 2-year-old child? That is my question. After all, in formulating a line of treatment, it really doesn't help us to say that if you give, say, 120 g. of protein and so much of calories, they get better. We are dealing with people who are malnourished and who cannot afford food. To us the question appears to be, what is the least amount of protein that you can reasonably give and bring the patient to a state of improvement?

Clements: I am not sure that that is the right kind of question. I should like to have that discussed.

Gopalan: If, say, by giving 50 g. of protein to a 2-year-old child, you can effect an appreciable improvement in 3 weeks, I think that is very much more important from the point of view of prevention than if we give 120 g. of protein. Perhaps I am stretching a point when I say the higher amount is harmful. I would have made my point if I said it was unnecessary.

Clements: Before Dr Dean answers that, I wonder if any of the fundamentalists here can help us?

Gyorgy: I can, sir. I am reminded, as a paediatrician, of one of the lectures I give all my paediatrics students every year. I acquaint them with the important analogy, coined 40 or 50 years ago by Czerny and Finkelstein, that in treatment we are between Scylla and Charybdis. Therefore, for very severe protein malnutrition we should not give too much but we should not give nothing, or too little. I myself in my paediatric career have seen patients with protein malnutrition, as we call it, whom people mistreated by giving too much protein or too many calories. I would warn very, very seriously about giving too much to a very severe case of malnutrition.

Cruickshank: They die?

Gyorgy: Yes, they die.

Dean: Have you ever given a very high protein diet to a child dying of kwashiorkor?

Gyorgy: I do not see much protein malnutrition in our temperate climate, but I do not think there could be any difference in principle.

Dean: That is where I differ.

Gyorgy: I feel that there could not be so much difference between your cases and the child who has been on a diet of starchy foods for many months and fallen into a condition of 'decomposition'—unfortunately, the German word 'decomposition' is a very poor one. At the stage of so-called decomposition a child does not tolerate calories or food in large amounts. You have to increase the food intake very gradually. If you don't give any food, or if you don't give enough food, you are in absolutely the same trouble. I personally have never seen any damage, because I am cautious and conservative. Generally I am not conservative, as you may believe, but here I am very conservative. I warn you as a fundamentalist, I warn all paediatricians very seriously, not to give large amounts of food to those children very suddenly.

Clements: I wonder whether Professor Gyorgy's warning doesn't relate to time, the time which you take to do things, rather than quantity? What is wrong with giving a child 100 g. of protein towards the end of treatment?

Gyorgy: Nothing. I meant a gradual increase. To begin with, when you are dealing with a markedly depleted child, you have to be very careful about pushing protein into him. You have to increase it gradually until you get above the level which he should have had in relation to his weight.

Clements: Then there is really no difference in what is being maintained.

Gyorgy: Yes, there is a difference, because Dr Dean claims that you should start with a high food intake.

Waterlow: Our experience is probably more in line with Dr Gyorgy's than Dr Dean's; that is to say, we find that we cannot increase the intake of the children very quickly. But I don't know why they should die or why they do badly.

Gyorgy: The general opinion has been that at first they have no enzymes for assimilation, and you are overthrowing the balance of the body with undigested and harmful products—partially digested food. You are overloading the body.

Waterlow: But what is the mode of death in these cases?

Gyorgy: Collapse and shock.

Waterlow: If you overfeed them?

Gyorgy: Yes.

Cruickshank: In the adult who is grossly malnourished, large quantities of food given suddenly will produce marked gastric dilatation with peripheral vascular collapse and death. It seems to me more a mechanical disturbance than a purely biochemical disturbance. Whether or not that applies to the child, I don't know, but that is what I saw happen in grossly depleted prisoners of war who were suddenly given very large quantities of food.

Gyorgy: I might add that the group that visited the Belsen concentration camp to investigate protein malnutrition found that even transfusion of protein hydrolysates caused the same thing—collapse and shock.

Mackay: When you say the body is overloaded with proteins, are you really meaning that the circulation is overloaded with amino acids?

Gyorgy: Well, obviously, when the amino acids were given by infusion. When proteins are given by mouth, we don't quite know. Maybe it is just a gastro-intestinal disturbance.

Mackay: Is this in part the explanation of the failure of these intravenous infusions of amino acids?

Clements: There seems to be a good deal of dissension with what I understand to be Dr Dean's regimen. Would you like to defend yourself, Dr Dean?

Dean: I gave Professor Gyorgy every possible opportunity of defending himself—

Gyorgy: In what respect did I not defend myself, I ask you, on this very pertinent question? Didn't I answer you?

Dean: You answered it and gave me the answer I hoped you would. The point is this—

Gyorgy: Wait, wait!

Dean: —I said, 'have you yourself treated severe cases of kwashiorkor with a very high protein diet?' and you had to admit that you had not. I am not a fundamentalist, but a person who has had very severe cases of kwashiorkor in his charge and has treated them in a certain way and has achieved certain results. Now, I have two objects in mind in my treatment. One of them is the experimental study of treatment, and for that purpose I started with these high doses of protein. What I have done ever since is to try to find the minimum amount of protein with which I can treat cases successfully.

As far as I have gone at the moment, I agree with Dr Gopalan, that probably the optimal amount of milk protein is something of the order of 10 g. for even the most severe case, but the milk proteins and the other proteins which I have to use are not, I think, of equal biological value; most of my experiments suggest that in spite of the addition of B_{12} and other vitamins, there may be some difference. I am not at all sure that 50 g. of any kind of protein would be effective; probably 25 g. of human milk protein would be as effective as 50 g. of cow's milk protein. I have not observed any ill effects whatever from giving 125 or 150 g. of protein a day.

Gyorgy: Not yet.

Dean: Although I have observed blood ureas up to 80 or 90 mg. %, I also found a real improvement in the child, which was dramatic and seemed to be better than had been achieved previously by the people with whom I was working.

Cruickshank: How many acute cases of kwashiorkor have you treated with this high regime?

Gyorgy: Severe cases?

Dean: About fifty or sixty. You will forgive me for saying it, but I am speaking of what I myself have done and observed. I tried earlier in this session to get people interested in the question of experimental treatment, but it would not be taken up by anyone. I want to know what we should do in the way of experimental treatment.

Clements: Has Dr Dean really got something you others haven't got? That question hasn't been answered yet.

Waterlow: Dr Dean, you put your babies straight on to the high protein diet as they come in, and they don't vomit?

Dean: I never see the cases until the morning unless there is some special reason. They come in during the day and are then put on glucose. The following morning we start off at midday with this high protein diet. On the first day, but only the first day, the usual intake of protein on this diet, which will provide 100 g., is probably about 40 or 50 g. On the second day it is probably of the order of 80 or 90 g. My rationale is this: we know that much of the food is not absorbed. How much can we get in at first? I give a great deal of protein to make sure that a small amount is retained in these crucial moments of the first days of treatment. Everything depends on the first days of treatment in our cases.

Williams: Don't the children ever vomit?

Dean: Sometimes, but vomiting is not a serious matter.

Rhodes: How do you get the food in? In Jamaica, with a severe case of kwashiorkor, we find it very difficult to get any food in. The child vomits when he is given more than a small amount of diluted milk, and if he does not vomit he passes it out in the faeces undigested. How do you overcome the terrible anorexia which we find so difficult? Do you force-feed them?

Dean: We never, in any circumstances, worry the child by trying to feed it with a spoon or anything like that, if it will not take it. We always use gavage if the child has any anorexia.

Mackay: May I attempt to resolve the difference between Professor Gyorgy and Dr Dean? It is well recognized by the workers in your group in Africa that the pancreatic enzymes are deficient. Am I not right?

Dean: At first the child has no pancreatic enzymes, but apparently it is able to pick up a little bit of the protein.

Mackay: In other words, I think you are doing what Professor Gyorgy suggests. You are giving a large amount of protein, which is simply not all absorbed.

Waterlow: But earlier you gave a figure of about 70% of nitrogen absorbed at the beginning of treatment, which seems to me very satisfactory.

Dean: That is over a 4-day period.

Waterlow: Yes, but still, it is 70%, not 20%.

Dean: On the first day it might be 20%. On the second day it would go up. But the whole rationale of my treatment is that the child cannot absorb well at the beginning; therefore give it every possible opportunity. I agree, in theory it may be a poor thing to do, but in practice it is a very good thing to do.

Mackay: Therefore, in practice, you are probably doing what Professor Gyorgy suggests.

Dean: Yes.

Gyorgy: How old were your patients?

Dean: One to two years.

Gopalan: May I ask a question about these other sources of protein? You said that they need 100 g., and that they may not do better on smaller amounts. Is that based on actual experience, or is that an opinion? Have you tried to give these patients less, and satisfied yourself that they do worse? My point is that even with these pulse proteins, you will do equally well with a smaller amount of protein.

Dean: I have experimented on the point, but, to my mind, that is an extremely difficult thing to establish exactly, and I do not have the figures that I would like to present to this meeting. My impression, for what it is worth, is that we have probably been giving too much protein and we can get equally good results with much smaller amounts; but please remember that I am trying to establish an experimental means of treatment, as well as to relate this to prevention. I am trying to do two things, and nobody else is doing this experimental work which is so vital.

Senecal: I would like to speak about our treatment of kwashiorkor, which is divided into two parts. The first part was last year, when we gave a normal diet with added protein and also vitamins and amino acids, but we did not get good results. Since the conference in the Gambia we have changed our method, and we now give at the beginning only protein, about 32 g. a day. Owing to anorexia we are obliged to give this solution of proteins by tube for 2 or 3 days. Then the appetite appears again, and the child begins to eat by himself. We then increase the calorie ration by adding carbohydrate. The results of this method are excellent. The skin lesions heal in 10 days, the levels of blood proteins, amylase and calcium increase, and we can follow the diminution of fat in the liver by biopsy punctures. After 1 month the child is discharged. We hardly ever see any relapses—only three after 2 months—but we have not been able to follow up discharged children who had left apparently quite cured. The three relapses were in a grave state, and two of them died as soon as they were re-admitted for the second time.

CLEMENTS: What I think has come out of this discussion is a challenge from Dr Dean's group. He has maintained that he does not get return cases. It is true that his period of follow-up is short. However, he says that he doesn't get any. The rest of you have had relapses on very much lower regimes. The other thing is that Dr Dean says his cases do not seem to suffer ill effects from their high protein intake, and he has a theoretical explanation for this. I think that the only way this can be tested out is not round this table by argument, but in the field, by practical experience.

WATERLOW: Dr Clements, may I suggest that one thing might be added to what you have said? As far as I know, the methods that Dr Dean has described represent the most careful scientific approach to the problem of treatment of anything that we have yet heard. I think that we have much to learn from him about the way to tackle this problem, quite apart from whether or not we agree with his actual methods. I am impressed by his thinking, as well as by his results (34).

GYORGY: I think both the Jamaican and the Indian groups have been frightened into complete silence about the treatment of V.O.D. in Jamaica and of biliary cirrhosis in India, which are both based primarily on protein malnutrition, if I am not mistaken. Could we not summarize it in one sentence, that protein therapy is satisfactory in both conditions, when it is given in the early stages?

RHODES: I have treated children suffering from V.O.D. with high protein diets and with ventriculin,* and my impression was that ventriculin was superior to a high protein diet. Unfortunately, treatment of the groups was not well controlled, and any definite conclusions have to be postponed until a well-controlled therapeutic trial can be done. This chart (Text-fig. 19) represents diagrammatically a selection of cases of V.O.D. treated in three different ways: with high protein alone, with ventriculin alone, and with high protein diet supplemented after a number of weeks by ventriculin. The high protein diet was a balanced diet containing about 60 g. of animal protein per day. Only two cases were given ventriculin alone without a preliminary period on the high protein diet. When ventriculin was added to the high protein diet, the amount of protein was reduced so that there was no total increase in protein intake.

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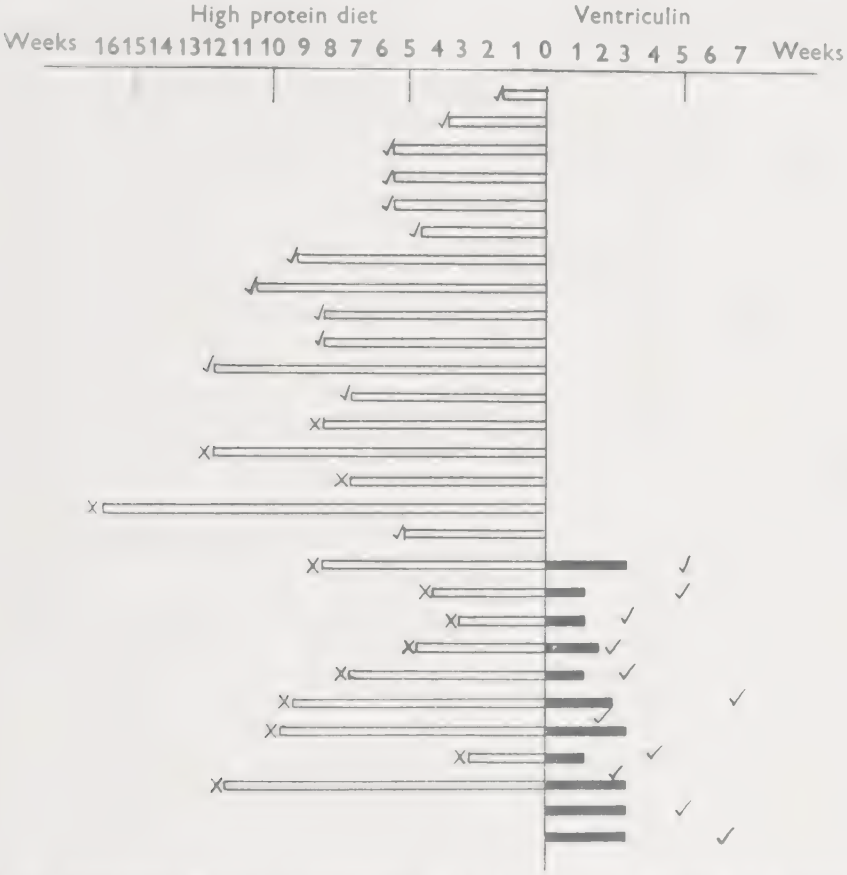
* The ventriculin was supplied by the courtesy of Messrs Parke-Davis, Detroit, U.S.A.



Text-fig. 19. Response of V.O.D. to treatment with a high protein diet and with ventriculin. The horizontal columns to the left of the line represent the duration of treatment with a high protein diet. The columns to the right represent the duration of treatment with ventriculin (10–30 g. daily). ✓, disappearance of ascites; ×, treatment discontinued with ascites still present.

I took the disappearance of ascites as the criterion of response to treatment, but invariably, coinciding with this, there was improvement in the liver function tests, particularly in serum albumin and cholinesterase, diminution in liver size and improvement of the child's general condition. Some children responded early, others late, and a few not at all.

There were four failures after 6–16 weeks on a high protein diet alone; thirteen others responded and were free of ascites within 6–14 weeks of starting treatment. Nine cases were on a high protein diet for 3–12 weeks and after that were given ventriculin, the total protein intake being maintained at the same level. These children were put on ventriculin because of little or no response to the dietary regime.

When we were rather short of ventriculin it was given in small doses for a short time—10 g. daily for 10 days. When we had plenty we gave 30 g. a day for 2–3 weeks. Except in one case, it was discontinued after 3 weeks, whether improvement was well under way or had not begun. All these cases were acute, of comparatively recent onset. All nine cases responded favourably to ventriculin and seemed to respond in a shorter time than those on a high protein diet, in 2–7 weeks as opposed to 6–16 weeks. Two cases were not given a preliminary period on a high protein diet but were immediately given ventriculin for 3 weeks; they were free from ascites after 6 and 6½ weeks respectively.

I know that many objections can be raised to these results, and that is why I said that the good effect of ventriculin is only a clinical impression and needs confirmation.

CRUICKSHANK: Surely the total duration of the treatment before you got a response was much the same in both groups, with or without ventriculin?

RHODES: Yes, that is true. But many of the cases, at the point when they were given ventriculin, were going downhill. Ventriculin was in such short supply that it had to be kept for those who were very ill and who did not do well on the high protein diet. Therefore yours isn't really a fair criticism. I will show you one case (Text-fig. 20 and Pl. 24). This child was observed over a period of 33 months, mostly spent in hospital. For 18 months there was no response to dietary treatment. The serum proteins fell, serum albumin was between 1 and 2 g. %, and the serum cholinesterase went down as low as 0·07 unit.* During that time the boy received oral and parenteral protein hydrolysates, and human plasma intravenously and subcutaneously. There was no improvement. This child had been an intelligent and alert boy, but he became completely apathetic, lost all his hair, his tongue was deeply ulcerated and he had practically no muscles. His abdomen was distended and required tapping every fifth day. He had oedema and appeared moribund. At this point a fresh supply of ventriculin arrived. He was given 30 g. daily, and within 10 days his blood chemistry and his general condition rapidly and very dramatically improved (Text-fig. 20). His tongue healed, his hair grew again and he changed back into a lively little boy. He was given ventriculin for 3 months. I saw him recently, 3 years later, and he was well, with a slightly enlarged, firm liver.

This second photograph (Pl. 24B), shows his appearance just before he left hospital. There was no ascites, but the abdomen was slightly protuberant owing to slack abdominal muscles, the result of overdistension by fluid for many months.

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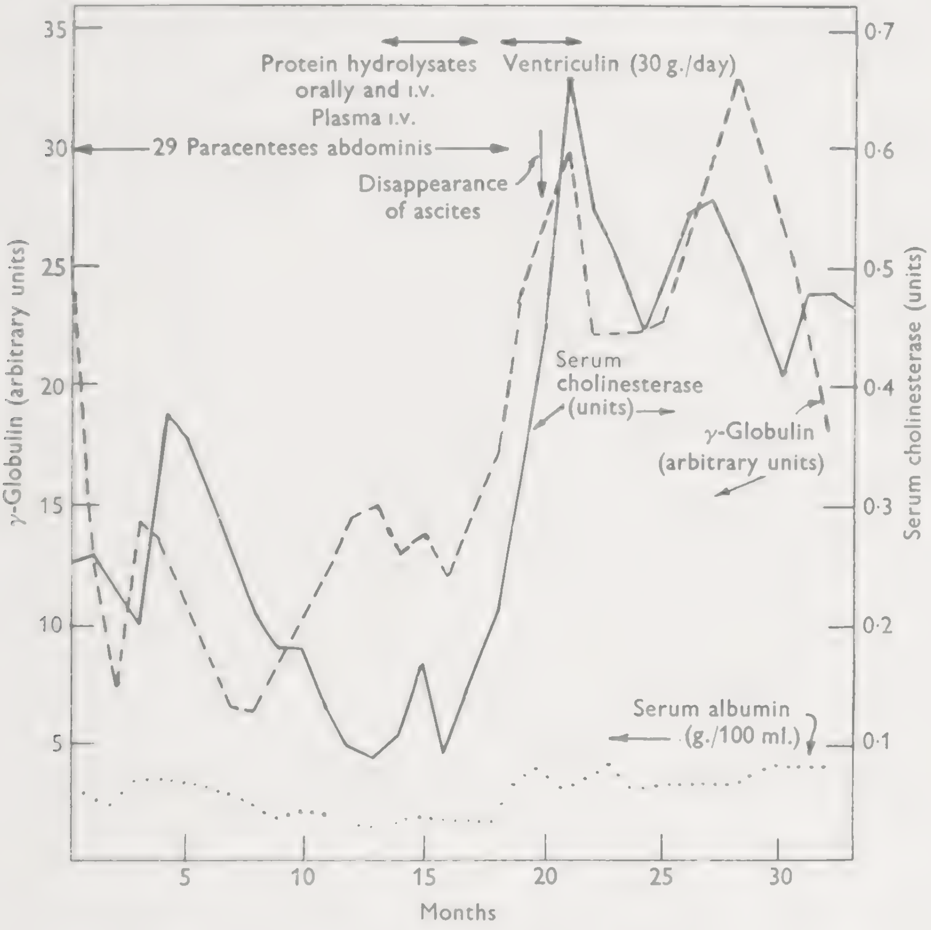
* Based on Michel units.

STUART: In assessing treatment it is important to take into account the stage of the disease at which treatment is started. Otherwise the results may be misleading.



Text-fig. 20. Response to ventriculin of a child with V.O.D. aged initially 1 year 10 months. See Pl. 24.

CLEMENTS: How do you treat infantile cirrhosis in India?

GOPALAN: I don't have any first-hand experience with infantile 'biliary' cirrhosis. As I explained we don't come across these cases in Coonoor. Professor Achar, who deals with cases of this disease in Madras, thinks that if he catches them in what he calls the early or preicteric stage, then treatment on a regime which is very similar to the one we use in kwashiorkor—just high protein and low fat—gives satisfactory results. But the treatment has to be prolonged over 3–4 months before anything like an improvement becomes manifest. If the cases come in at the stage when ascites and jaundice are already there, they mostly end fatally.

CLEMENTS: Thank you. I am now going to ask Dr Rao if he will sum up and answer the questions that have been posed about clinical features and treatment in the spirit: 'Where do we go from here?'

SÉNÉCAL: Mr Chairman, I am sorry to say that I am obliged to leave today, and I want to thank you and every member of the Conference for this interesting discussion.

SUMMARY

RAO: Following the lead given by Dr Waterlow, I considered it profitable to discuss individual signs and symptoms in cases of protein malnutrition, with the hope that this would lead us to processes, instead of considering the disease entity as a whole. My main object was twofold: first, to obtain further information about the clinical aspects of the syndrome; secondly, to elicit local variations in the signs and symptoms and the factors which influence these variations.

There was a frank exchange of views, which has given a clearer picture of the syndrome than we had before. I shall now catalogue the discussion on the various symptoms, one by one.

Oedema. The onset, distribution, and severity of oedema were discussed at length, in view of its importance. While oedema is usually present at some stage or other of the disease, there may be cases where it is absent, especially in the earlier stages. The oedema may be gradual in its onset or precipitated by infections and diarrhoea, and may or may not be related to the severity of the disease. The relation to hypoproteinaemia is also variable. Evidence has been presented that in community surveys swelling of the dorsum of the feet may be the earliest sign, long before anorexia or the other signs and symptoms appear. The oedema appears usually in the following order: on the feet, then on the legs, face, especially under the eyes, and the hands. In some cases it may be generalized. Sudden onset of ascites has been described in the Jamaican cases of V.O.D.

Growth. Several workers have observed retardation of growth in cases of protein malnutrition. It was fully realized that there are fallacies in taking body weight as an index of growth, especially in view of the presence of oedema, intestinal parasites, and undigested food in the gut. Even when allowance is made for these factors, there is evidence that there is diminished body weight in the children who show symptoms of protein malnutrition compared with either the accepted standards of other countries or the local standards in the particular area. Environmental factors may play a part in local differences noticed in different parts of the country. Retardation of growth was a noticeable feature in the Jamaican children showing hepatic enlargement. While loss in body weight may have no significance by itself, when taken in conjunction with other signs and symptoms it may be considered as additional evidence of protein malnutrition in children. Although small differences in weight may not be considered as important, even small differences in height assume great significance in the study of the syndrome.

Skeletal development. There has been no clear indication of retarded skeletal development in cases of uncomplicated protein malnutrition in children. However, evidence has been presented to suggest that this aspect requires further investigation.

Skin changes. The skin lesions have been discussed at length, and in general the description of the various lesions and their distribution is similar to those which have already been presented and with which all of us are now familiar. One point which deserves mention at this stage is whether local variations in the skin lesions are in any way influenced by local variations in the dietary habits of the children and in the supplementary foods given to them, especially the nature of the cereal in their diet.

In view of the close similarity of some of the skin lesions to those of pellagra, the question of niacin deficiency in the aetiology of the condition was also discussed. Evidence has been presented that the skin lesions respond remarkably well to a high protein diet alone. The severity of the skin lesion appears to bear no direct relation to the severity of the disease. Some of the cases of protein malnutrition in children may not present any of the lesions described.

Changes in the hair. As in the case of skin lesions, the changes in texture and colour of the hair have been described, and it has been pointed out that there is no direct correlation of these changes with the disease process as a whole.

Onset of the disease. Some of the weaning practices were discussed at this stage. It was pointed out that the age distribution of the disease is identical in different regions, in spite of great differences in weaning practices. Although no definite evidence is yet available, there appears to be a long latent period before the appearance of overt clinical signs. During this period the weight curve may show a tendency to fall. Diarrhoea and anorexia have been the first symptoms in some cases. Mention has already been made of the swelling of the dorsum of the feet observed by some workers as the first symptom of the disease.

Facies. Circumoral pallor and bagginess of the cheeks have been particularly stressed as striking changes in some of the cases of protein malnutrition. Their exact significance, however, needs further study.

Anorexia and diarrhoea. Diarrhoea may be the presenting symptom in some cases, and the precipitating factor and the cause of oedema. While there appears to be no close correlation between protein malnutrition in children and the incidence of diarrhoea, it has been pointed out that diarrhoea can be a feature of the disease. The occurrence of steatorrhoea in cases of protein malnutrition in children, even when there is no fat in the diet, has been discussed, and further work seems indicated to find out the source of this fat.

Lassitude. While lassitude has been described as an early symptom of protein malnutrition in children, its occurrence in other types of malnutrition has been pointed out.

Liver. The incidence of enlargement of the liver varies considerably from place to place. In Jamaica it is quite common, while in other countries, especially in Africa, liver enlargement is not a noticeable clinical feature. The clinical enlargement of the liver is probably due to an increase in fat and water content of the organ and a decrease in the protein content.

Infections and infestations. The problem of parasitic infestations has been briefly discussed, and attention has been drawn once again to the study of factors complicating the clinical picture in cases of protein malnutrition in children.

Treatment. Then, coming to the question of treatment, the importance of utilizing locally available foods has been stressed once again. The use of skim milk, calcium caseinate, and preparations containing soya bean and banana, or Bengal gram, jaggery, and banana has been described. In general, while the response to the administration of vegetable proteins has been quite satisfactory, there appears to be a slow regeneration of the plasma proteins on the vegetable regimen. The beneficial effect of vitamin B_{12} in treatment has been suggested, and further work may throw light on this problem.

While blood transfusion and plasma transfusion have been indicated in severe cases or in cases of incessant vomiting, their use as a routine measure has not been advocated.

The beneficial effect of a high protein diet, with or without ventriculin, in cases of V.O.D. and in infantile cirrhosis has been discussed briefly.

Recurrence of protein malnutrition in children after discharge from hospital has been mentioned, and there has been quite an interesting discussion as to why there should be variations from one place to another; this further brought out certain lines of treatment. It has been pointed out that the administration of protein in large amounts must be slow and cautious.

I have nearly come to my journey's end. That summarizes the discussion which we had in the third session. While I am perfectly satisfied that we are on the road to progress and that we have made considerable advances since we met in the Gambia. I feel that there are a number of gaps still which have to be filled; in summarizing I thought this would be a good opportunity to indicate where we should go from here.

One of the things which was very remarkable and striking is this: that all our material or nearly all has been drawn from hospital cases, so that we are dealing with a syndrome which we see in the later stages. That has given rise to certain misapprehensions as far as the earlier signs and symptoms are concerned. Surely a disease process which you see in the later stages must have some beginning somewhere, and it is this with which we are confronted.

I am a clinician by inclination, but a public health worker by practice at present. To us the problem is of the utmost importance. We ask: What is the incidence of the disease? But that puts the cart before the horse. How are we going to detect the earlier cases? That is where the clinician and the biochemist have to put their heads together.

Yesterday we touched briefly on weaning practices. Further work is necessary to find out what exactly the maternal diet is. I remember, in the Gambia, it was Professor Gyorgy who raised a fundamental problem, that apart from quantitative deficiency of protein, there was the question of qualitative deficiency of amino acids in the protein. The mother's milk may be deficient in protein, but still may be able to supply some essential food factors, and therefore it is of the utmost importance not only to study the quantity but also the quality of mother's milk. Since we left the Gambia some of us have been working on the amino-acid composition of mother's milk, not only of healthy mothers but also of mothers who are malnourished. That is a problem which it is worth while taking up before we proceed further.

While briefly outlining the treatment, mention has already been made that local foodstuffs have to be utilized in the treatment of the disease. It is up to us to find out what are the various practical measures to be taken along these lines. I would briefly touch on the study of environmental factors, especially of the different changes in the skin and hair from place to place.

These are some of the problems which I have posed for you, and for want of time I shall not proceed any further. I have, however, tried to present the highlights of the discussion, which have a bearing on further investigations on the problem of protein malnutrition in children.

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FOURTH SESSION

EPIDEMIOLOGY AND PREVENTION OF PROTEIN MALNUTRITION

CLEMENTS: I am going to ask Dr Dean if he will open this session, which will be devoted to epidemiology, aetiology and prevention.

DEAN: There is lamentably little exact knowledge available about the disease called kwashiorkor, and most of what I am going to say is put out in the hope of eliciting information. I want to learn. Recently I have been trying to collect the literature, and I ran into very great difficulties over the question of nomenclature and adequate description. I just don't know what people are talking about. We called our book *Kwashiorkor* because it is a widely accepted term. It is not really intended to be a specific name.

GYORGY: I am afraid that this conference equates protein malnutrition and kwashiorkor, and I think that is wrong.

DEAN: It wasn't until I came here that I thought anyone equated protein malnutrition and kwashiorkor.

GYORGY: But here the impression is created that they are equal.

DEAN: Yes, that seems to have been accepted here. I imagined that everybody wanted to equate them, so I didn't raise any objections, out of politeness to the rest of the audience.

GYORGY: Well, I am glad to have you make the correction.

RAO: I would refer to the Gambia Report (1) in which we agreed that in order to avoid ambiguity and until more knowledge is available, we should stick to the term 'protein malnutrition', for want of a better; there is no name which is universally accepted, not only in Africa, but also in different parts of the world. Therefore, I would suggest that we stick to this name 'protein malnutrition'.

AYKROYD: Surely we are coming now to the broad consideration of incidence and prevention, and are thinking of protein malnutrition in its broad aspects, one of the manifestations of which is kwashiorkor. Am I right that this is our concept in beginning this discussion?

RAO: We must not limit the discussion to one condition alone. Against the broad background we might discuss the subtypes, including kwashiorkor. But the problem is much wider than kwashiorkor alone.

GYORGY: That's right; they are subtypes. For instance, V.O.D. is a subtype of protein malnutrition.

WILLIAMS: I would suggest, from what I have seen in Uganda, that Dr Dean is generally dealing with the kwashiorkor subtype.

RAO: We are trying to enunciate the broad principles of prevention and treatment of protein malnutrition in children all over the globe, call it by whatever name you want.

GYORGY: And starvation is protein malnutrition, obviously.

RAO: I think, as a compromise, Dr Dean, you can describe your cases as a type of protein malnutrition.

DEAN: Good, I will proceed then. I think it is true to say that it is rare for kwashiorkor to appear in a child who is on the breast; when it does, it is probably because the amount of breast milk available is very low, and probably there must be some other conditioning factor as well.

GYORGY: You have kwashiorkor in your breast-fed infants?

DEAN: No, not in my cases; I was talking about the literature.

GYORGY: Well, as far as I know, with the exception of perhaps one case of Professor Platt's, which had malaria, no case of kwashiorkor has ever been seen in infants receiving nothing but breast milk in sufficient amounts.

DEAN: I would agree with that, but from my survey of the literature there seem to be a certain number of cases described in children who were still on the breast. Presumably, as you yourself emphasized, it is a question of the amount of milk obtained. Children do not get kwashiorkor when they have an adequate amount of breast milk. Not only breast milk but also cow's milk seems to be effective in preventing it. I think that Dr Autret will agree that he never saw kwashiorkor in the Masai tribes in Africa that he investigated with Dr Brock, if the milk intake was adequate.

AUTRET: That is true. We have not seen kwashiorkor in pastoral tribes (2).

DEAN: We have the Hima tribe in Uganda, who live largely on milk, and no kwashiorkor has been observed amongst them, although quite a careful search has been made for it. In the vicinity of Dakar kwashiorkor is to be found, but not in any child who has been known to have any milk.

GYORGY: Any milk? Would you specify, perhaps?

DEAN: Cow's milk.

GYORGY: Yes, but do you mean one teaspoon, or what was the amount necessary to prevent it?

DEAN: Dr Bergouniou (3) says that if the diet of the child contained cow's milk—he did not say how much—he could not find kwashiorkor.

GYORGY: I'll wager a bet that with one teaspoon of cow's milk and the ordinary diet, you will get kwashiorkor.

BRAS: I have a reference saying that in two hospitals in Senegal 9% of the partially breast-fed children had kwashiorkor.

AUTRET: The criteria adopted in Bergouniou's survey (3) on kwashiorkor in some population groups in Senegal are not the same as the ones you would accept. Some cases reported as kwashiorkor are only under-nutrition, with an enlarged liver and without the slightest oedema. No measurements were made of plasma proteins.

CLEMENTS: Equally, people talk about breast-fed children, but don't indicate how much milk the child is getting. As I said the other day, is the breast being used as a source of nutrient or is it being used as a comforter? Until we have that information along with the clinical picture, we are only guessing.

AUTRET: One of the cases of kwashiorkor observed by Bergeret in Dakar was a child at the breast who was not given any other food. I also saw one such case in Feshi, Belgian Congo; both the mother and the child had kwashiorkor.

DEAN: We tried, by questioning the mothers very carefully (4), to find out what the children were having. We came to the conclusion that the poorest of our mothers was never able to afford any cow's milk, although we never found any mother who did not admit that she was able to buy meat once or twice a week. The only thing that seemed to distinguish the poorest mothers from all the others was this inability to buy milk, and not any other food about which we asked.

There was an illuminating remark by Donnelly (5) from the Gold Coast, who translated a local saying, which perhaps Dr Williams will confirm, to the effect that 'when parents are poor, the infant cannot get any proper substitute for its mother's milk and so gets the sickness'.

WILLIAMS: I should like to correct the saying, as one often has to. 'It is not the quantity of money or of other things that is lacking, it is poverty of knowledge of what to buy.'

GYORGY: Milk is more expensive than meat? Probably not.

WILLIAMS: No, but they don't know how to feed. They don't realize the requirements of the child, although they have plenty of food.

AUTRET: Behar and I saw in one Central American country a child with severe kwashiorkor. The mother told us that after a period of diarrhoea the child had been fed for 3 weeks on a well-advertised beverage, and received practically no other kind of food. A small bottle of this product cost as much as one quart of milk.*

DEAN: I think, too, that we must consider catastrophes which upset food supplies. I remember Pieraerts in the Congo telling me that he thought the incidence of kwashiorkor varied directly with the extent to which cassava had to be resorted to. It is used as a famine crop there, as it is in many other parts, and he was quite convinced that more cases turned up after the people had had to live on cassava for some time. Now, here I know you have hurricanes, and I wonder if you have been able to observe any effect on the incidence of kwashiorkor from the disturbance of food supplies caused by hurricanes.

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* Dr Abbali of Havana informs me that some cases of kwashiorkor in Cuba had been fed on beer.—J. Waterlow.

Gopalan: We have observed a correlation with floods created by outbursts of monsoon, because the floods interfere with the transport of food and, also, I believe, favour the development of infections. In the wake of the monsoons, particularly if they happen to be very severe, as they often are on the West Coast, the incidence of kwashiorkor seems to rise.

Mackay: We have tried to observe the influence of a hurricane on the general nutritional status of a group of children in a small valley here in Jamaica. We had about 200 children there who had been under observation for about 12 months. When the hurricane came it completely cleared out all the food-bearing trees, and the torrential rains removed almost all the ground food crops. The hurricane was followed by a drought. Therefore we have here a small group, which, in a sense, has been experimentally starved. Our results are now being examined and will be published shortly.

Dean: Are you considering the possibility of the rise of infectious disease? It is a very important point that Dr Gopalan made, because the effects of a hurricane are not limited to the food supply.

Mackay: No, we are not.

Autret: The first time 'bouffissure d'Annam' was officially reported, it was in an area of Northern Annam which was isolated every year by floods. Normet(6) described it later in the same place; a high incidence of cases recurred every year when severe typhoons struck that part of the coast of the China sea. That lasted until the railway was built in 1933. After 1933 such outbreaks of severe protein malnutrition were no longer seen. Supplies of food were brought by train and the region was no longer isolated after typhoons.

Williams: I think the same thing happens probably every year in Jamaica. In our study of vomiting sickness(7) we found that the average death-rate for the whole island in the first 3 months of the year is 25% higher than in the next three-quarters, when there are plenty of bread-fruit, root vegetables, and mangoes. Even the infantile mortality goes up 25% during the first 3 months. There is also a big incidence of influenza. But we haven't examined in detail the influence of age, locality, or what the diseases are that cause this increased death-rate.

Dean: It would be very interesting to find out exactly what causes it.

Williams: Yes, and to find out what brings the rate down.

Aykroyd: You might also include, Dr Dean, economic blizzards. Dr Chavarria has told us about the price of coffee and its relation to the disease in Costa Rica.

Dean: Yes, that is obviously important, because, as I shall try to point out, this problem cannot be divorced from its social and economic aspect, as I am sure you would be the first to state.

The feeding of a tropical community is a hand-to-mouth affair, quite different from the feeding of a community where there is facility for storage of food and a more or less continuous stream of the same kind of food all the time.

In Uganda storage is limited and difficult, and it must be so in many other places. But under these conditions it should be possible to get some exact idea of the relation of the incidence of kwashiorkor to food supply, and that is why I raise this point at the moment. There have been some observations in Kenya, which is next door to Uganda, in which it was found that in April to August, when millet was being eaten, the incidence of kwashiorkor was very low. In August, although the millet was becoming exhausted, maize was available and the incidence of kwashiorkor remained low until the end of the year. In November and December there was a rise in the incidence as the maize, in turn, was getting exhausted. In January, the incidence went down because the bean crop came in. The situation deteriorated again in March, when there were no more beans left. They are eaten rather quickly and are a fairly small crop. The millet wasn't ready and there was no other food, and then there was a very high incidence of the disease.

Gyorgy: What do they eat?

Dean: What is left over. Amongst other things, they have plantains there, but they do get some maize. There is some cassava, too, but I don't think there is any other high-protein crop at that time.

Scrimshaw: In Central America, where corn plays such an important role, these correlations are quite pronounced; in Guatemala, where they use yellow corn, you can follow a sharp drop in the carotene content of the blood as the price of corn rises towards the end of the dry season. You can readily detect severe economic conditions or famines, brought on by drought, because rural people substitute sorghum for corn and make their tortillas from sorghum. That is the height of disgrace, and they won't admit it easily. That is the time when some of these nutritional conditions become most prominent.

Clements: Don't beans form an important part of the diet there as well?

Scrimshaw: According to surveys made by I.N.C.A.P., about 60% of the protein comes from corn in Guatemala and a little less in El Salvador. 18% comes from beans in Guatemala, and 28% in El Salvador.

Autret: Statistics on agricultural production show a consumption of beans ranging from 30 to 60 g. per head per day in the different countries of Central America. However, dietary surveys made by F.A.O. in urban and rural communities of the same region show an average consumption varying from 50 to 90 g. per head per day. Of course the distribution within the different members of a family varies enormously.

CLEMENTS: Isn't there a price differential between maize and beans, which means that the poorer people would buy less of the beans and more of the maize?

SCRIMSHAW: That is partly true. However, for the Guatemalan Indians their whole culture and religion and economic system are tied to corn, so that its use is not determined by economic considerations alone. You can't make tortillas out of beans; that is what it amounts to.

DEAN: There is one point on which I would like to have your advice, Dr McCulloch. I refer to the work of Gelfand (8), in which he said that the rainy season in Rhodesia saw the highest incidence of kwashiorkor, and that led him to think that the origin of kwashiorkor might not be nutritional. But isn't it truer to say that the rainy season is also the season when food is in short supply?

MCCULLOCH: Very definitely. That is when prices go up. In northern Nigeria they wait for the first rain before they dare plant, because the seasons are so variable. That is the time when the storehouses are empty; they are scraped to the bottom until the next crop comes in.

PEÑA CHAVARRIA: In Costa Rica the same thing happens. We have a very sharp division between dry and wet seasons, and as a rule our malnutrition rate begins to rise about 2 months after the rainy season starts. We think it is not due to the crops themselves but to difficulty in transportation between one place and another; the roads are bad and become impassable on account of the tremendous rainfall.

SCRIMSHAW: Our results show a 2-month lag before the blood levels of vitamin A and riboflavin begin to rise after the beginning of the rainy season. We believe this to be associated with the decrease in price and increase in availability and use of fresh vegetables as the rainy season continues.

VERGARA: In the southern part of Chile there is a considerable drop in milk production during the winter, which is very long and cold, and that is just when you get an increase in the incidence of protein malnutrition.

DEAN: I have been interested by the fact that Curaçao is a completely desert island and that all its food has to be imported from elsewhere; yet Dr Van der Sar, in his first account, I think, was able to report a seasonal incidence (9).

VAN DER SAR: Yes, there is a definite seasonal incidence.

DEAN: That being so, it seemed to me a way of getting at the cause of kwashiorkor, because you could go down to the harbourmaster and ask what food had been imported.

Van der Sar: We think it is a question of rain. The incidence is high in the rainy season, when we have more flies and more dysentery. We think the cause of the outbreak of kwashiorkor is the infections which arise at that time in Curaçao.

Dean: I am glad to have that opinion, but are you quite sure there is no seasonal variation in the importation of food?

Van der Sar: No, there is no difference, absolutely none.

Dean: That is a valuable point. Do you get any milk?

Van der Sar: Milk is imported in cans.

Dean: There is more milk imported now than formerly?

Van der Sar: I have no figures available but in general the people are getting more milk-minded. We have maternity clinics and we have been teaching the people how to use milk.

Dean: Is there any correlation with a change in the incidence of kwashiorkor?

Van der Sar: Yes, I think so. The disease seems to be getting less common.

Autret: In the Belgian Congo kwashiorkor appears at the end of the dry season, just before the start of the seasonal infections. That has been shown by Pieraerts.

Dean: I think this point about the rainy season or the cold season is rather important in another way; it might cause the appearance of one special sign, the skin lesions. The Gillmans (10) pointed out that there was a seasonal variation in the skin lesions of pellagra, and those of kwashiorkor are pellagroid. There may be some connexion with the trauma of cold weather.

To sum up the discussion so far; we agree that deprivation of food leads to a high incidence of kwashiorkor, and it seems possible that the deprivation involves the protein side of the diet.

I think we should go back now to human milk, and discuss very briefly the normal course of lactation. It seems fair to say that breast milk appears to be designed by nature to be fully adequate only for a short time.

Gyorgy: How do you know it is so designed by nature? What is the basis for your statement?

Dean: I think it is reasonable to say that there is a term for lactation. It seems to be so in domestic animals, and I think it is probably so in humans. The point is this, that if breast milk is only fully adequate for a limited period, then after that time we have to find something else to secure optimum growth, and here we are straight in the middle of the problem of kwashiorkor and its prevention.

GYORGY: I have to interrupt you again, Dr Dean. What is optimal growth?

DEAN: That is a very difficult question.

GYORGY: But you used the term.

DEAN: I did. It was brought home to me very vividly yesterday by Dr Aykroyd, who pointed out that in nearly every under-developed community which has been studied, the children grow superbly for 4 or 5 months, and then the average weight gains fall off, compared with the weight gains in European or American countries. When I said 'Why?' he said 'Well, which is the right one? Which is optimal? Is it better to go fast, or is it better to go not so fast?' That is partly, I think, a philosophical problem, but partly a very important practical one, if you believe the results of rat experiments, which show that the fast maturing rat tends to have a shorter life. However, I don't want to go into the subject of whether it is better to have a long life or a short one, of whether or not accelerated development is a good thing.

SCRIMSHAW: That point, however, is certain to come up again and again when we talk about feeding, especially when we talk about supplements of vitamin B_{12} or antibiotics, and measure their effects on growth. Improvement of growth seems to be an invariable accompaniment of improved nutrition in people previously malnourished.

Whether this increased growth is good or bad, we have to take it as a *consequence* of better feeding and improved general nutrition, and because of the constant association it also becomes a *measure* of improved feeding and improved nutrition.

GYORGY: That argument may be fallacious. In the States several paediatric schools have recommended that the premature infant, for instance, should be fed cow's milk instead of breast milk, even in the first 4 months of life, because he will grow better and gain faster. This, therefore, is the question that I am always asking: 'Is this steeper weight curve better for the child?' And I don't receive any answer. I don't have one myself either.

AYKROYD: Surely we must accept the fact that to have a steadily rising growth curve, such as is characteristic of the best-nourished children in North America or Europe, is a better way to proceed through life than to have a curve which 'plateaus', say, at about the sixth month. I don't see why we need argue that point.

DEAN: I think that is a perfectly reasonable statement. There is one other very important point arising from what Dr Scrimshaw has said; I am frequently asked to find some way of assessing the nutrition of a child or a group of children at a particular moment. I have come to the conclusion that the only reliable test is to take those children and put them on a diet which is complete in every way, and see if their growth rate increases. If it does, I think that they have probably been undernourished up to that time.

SCRIMSHAW: That, of course, is the aim of all of us in our many different situations. Later on I shall present some evidence that the children of Central America respond very rapidly to extra food, and that we are not dealing with a genetic retardation in growth but with a real nutritional phenomenon of which retarded growth is an indicator.

DEAN: Feeding a child with growth failure due to kwashiorkor does not produce the same kind of result as we got in German children who were undernourished. But in the one or two children whom I have been able to feed for a long period after they had had kwashiorkor, I have been surprised to find that they achieve weights, if not heights, which are nearer to European standards. I agree with you about genetic limitation on growth. We can talk about that much too glibly.

To go back to the question of the supplementation of the diet when the mother's milk is failing; in western countries the usual supplement is, of course, cow's milk, and much of our medical thinking has been based on that simple fact. But if you measure the diets of children who are living on a mixed diet in a country like England before the recent war, you find that they exchange the breast-milk diet, with perhaps, 9% of calories derived from breast milk protein, for a diet which has 13 or 14% of calories from protein.

GYORGY: It is less; in the breast-fed baby it is between 6 and 7%.

DEAN: Well, that makes my point rather more pertinent, because in the measured diets which Dr Widdowson recorded (11), the amount of protein in the mixed diet provided 13 or 14% of the calories. I am bringing in these figures only to point out that when the baby comes off this wonderfully beneficial milk—human milk—you must make a tremendous change in its diet to achieve anything like regular growth.

GYORGY: And why is that?

DEAN: I imagine it is because the mixture of amino acids or the quality of the protein that you can supply is inferior to that supplied by human milk, which I consider to be well adapted for human nutrition. Is that a reasonable answer?

GYORGY: I would like to come back to that this afternoon, maybe.

DEAN: But I think it is also worth pointing out that for the majority of the people in the world the use of cow's milk in this way must be extremely recent. It was only a year before the last war that in England we were able to ensure that every child, or almost every child, got some milk every day. But the use of milk, which has influenced our paediatric thinking to such a large extent—and we have been brought up in countries where milk is plentiful—can only be of extremely recent origin. I think that in former times cows must have been kept by very few people, and perhaps were used for their children, but that the ordinary person had very little chance of obtaining milk (12).

I have been struck by the way in which the older paediatric literature, going right back to the seventeenth century, in England at least, condemns the use of *mil de pain*, which was usually bread boiled in water, with this or that added (13), but in essence a kind of soup made with bread and very little else. The paediatricians recommend that if you had to use that for the supplementary feeding of your child, you should add to it some cow's milk or the milk of other animal. The fact that they were always so insistent upon the necessity for adding milk is one reason for believing that usually milk was not used, and that they were well aware of the effect of feeding a child on a diet to which milk was not added in that way.

In the underdeveloped countries the supplement which is given to the child is usually the unmodified adult diet, and I don't know of more than one or two instances of an underdeveloped country which has any special means of feeding its very young children. I would like very much to know of anyone who has heard of special preparations being made, in primitive communities, for the use of young children.

Burgess: Do you say the unmodified adult diet, Dr Dean? It is usually only a portion of the adult diet, isn't it? Usually the worst portion, because it is only the soft food that the child can manage.

Dean: Certainly. What I should have said, perhaps, is that the diet is not specially prepared for the use of a child. Dr Autret did give me some details of a bean preparation used in the Ruanda Urundi.

Autret: Yes. Boiled beans in water; in some places there the water, or the broth, is given to the child very early. I was even told of one tribe in which the children were never breast fed; from birth they were given cow's milk only. In another tribe in Urundi very young infants were given a rather elaborate preparation including banana juice, various vegetables and water in which fermented sorghum had been cooked.

Williams: In most countries where it is not the habit to wean children early, lactation does continue longer. The child is getting some milk from its mother up to the age of 3 or 4 years. This provides a small supplement, which, it is true may not be very effective if the mother is badly fed. In places like Burma you will see a child of 4 years suckling.

Clements: Can we keep the record straight and say that the child suckles at the breast in these countries?

Williams: I have expressed milk from the breast. There is definitely milk present in many cases. I have frequently examined them.

GOPALAN: Speaking of this prolonged suckling, even in India it is the habit for mothers to go about suckling their children for a period of 2 years. We believe that this prolonged suckling can have nothing more than a comfort value. We have actually tried to express this milk and to determine the 24-hour output, and in a few cases where the suckling has gone on for 2 years, the output was from 12 to 42 c.c. in 24 hours. Therefore, I don't think that the prolonged suckling has any nutritional significance.

DEAN: It may not have.

WILLIAMS: I think it depends on what people you are talking about, because in some of these mothers whom I have examined, there has been milk. It may be dependent on the nutrition of the mother. In places like the Gold Coast there is practically no poverty; there is plenty of food and the mothers are well nourished, vigorous and full of energy. Very often I examined the breasts of women who had not had a child for 8 or 10 years, and there was still secretion there.

CLEMENTS: Yes, but is it milk as we understand it?

WILLIAMS: I don't know what you understand by milk. It looks like milk. I'm sorry, but I haven't done any laboratory analyses. The only analyses I have were of fat content. I think it depends a good deal on the nutrition of the mother; just as a Jersey cow can go on lactating between calving, I think these women can. It is a question of supply and demand. I think that many people will secrete milk if there is a constant demand, so that it is non-stop nutrition in some of these cases.

CLEMENTS: How much milk, do you know?

WILLIAMS: No, I couldn't tell you.

CLEMENTS: How do you know children get any under such conditions?

WILLIAMS: Because of the habits of the people; that is, the women were living together in compounds, and the baby would be breast fed regularly until the mother was pregnant with the next child. She would then begin to wean it, but if the baby was screaming or hurt or was worried, the grandmother or somebody else would give it the breast. In some cases the breast was merely a dummy; in other cases it was a good lactating breast. It was impossible to estimate accurately, but in a great many of them whom I examined, there was some secretion present. I remember a grandmother who was able to produce some milk, although it was 18 years since her last child.

DEAN: Dr Waterlow, haven't you some figures?

WATERLOW: Most of my cases in the Gambia were about 18 months old. According to our measurements, they were getting about 15 ounces of milk a day from the breast.

GYORGY: That is fairly satisfactory.

WATERLOW: Fairly satisfactory, but not completely.

Dean: What you did was to take the amount of milk present on one occasion and multiply it by the number of times the breast filled up?

Waterlow: No. The baby was test-fed throughout the 24 hours, being separated from its mother between feeds. This, of course, was abnormal. There might be a small amount of vomiting and we couldn't be absolutely certain we got every scrap of milk.

Dean: Still, that is a considerable amount, isn't it?

Waterlow: As Professor Gyorgy said, it is not bad. But we didn't do many cases. I wouldn't like to put too much stress on our results.

Clements: Miss Massal, who has been working for the South Pacific Commission, has been trying to measure the amount of milk available to infants from mothers who offer them the breast. She arranged to feed the infant artificially for 24 hours and endeavoured to express the total amount of milk secreted. The results obtained for New Guinea women were of the following order (14):

Age in months	No. of babies	Milk secreted	
		Range (oz.)	Average (oz.)
11–13	19	4–27	13½
14–18	21	2–22	10¼
19–24	14	¼–21	7
24–27	18	0–10	3

Hill: One other complication is that a woman may suckle more than one child in the family. In Indonesia we observed that women may suckle children 3 or 4 years old. If they suckle the child at 3 years of age, are they also suckling the child at 1 year?

Williams: If there is a younger child they will be suckling that, but the other child may have a pull occasionally. Among many of these people there is a sort of community feeding programme, in which anybody whose child may have died—as often happens with the enormous mortality—takes on another child. There was one woman who came to me in the clinic in the village who had had a baby which had died 3 months previously. She was still pouring out milk. She went about with two cigarette tins tied into her clothes because she was dripping constantly, and she wanted medicine to control the lactation. I tried to get her to come to the hospital as a perpetual wet-nurse, but there was a very strong taboo. Only women of one's own family can suckle the children.

Aykroyd: All this, while very interesting, does not seem to me to affect Dr Dean's original point, that after a certain age, say, 6 months, the average mother in the average underdeveloped country is unable to produce enough milk to permit the child to grow in the normal way.

CLEMENTS: You are quite right.

DEAN: Yes, I think we can go further than that. The discussion has suggested that the incidence of kwashiorkor might depend upon the degree of success in supplementing this failing lactation.

WILLIAMS: And the quality of the milk, which I don't think has been investigated.

DEAN: The quality has been investigated. It is a difficult thing to do. There was one report which I think Dr Autret mentioned, which certainly demands repetition, in which it was suggested that the amount of sulphur-containing amino acids was low in undernourished mothers.

AUTRET: We have some figures given on mothers' milk in Dakar, by Auffret & Tanguy (15) which show that the methionine content is low. However, there was no control done on white women living in Dakar and the figures obtained by a colorimetric method were compared to figures obtained in Paris. The comparison was not made on milk after equal periods of lactation. Furthermore, the methionine content is related to the amount of the different milk proteins (casein, lactalbumin, globulin), the amounts of which vary as lactation goes on. In cow's milk, for example, the casein increases and the lactalbumin decreases. The composition of the two are different. Casein is richer in methionine. But is it the same in human milk?

DEAN: Moreover, the total amount of protein in the milk tends to drop throughout the period of lactation.

AUTRET: Yes. But this is not very marked in human milk in Africa. Jelliffe (16), in Ibadan, has found that there was no apparent diminution of the milk protein content with prolonged lactation, and Dufour & Gourry [illegible], in Dakar, have reported only a slight decrease.

SCRIMSHAW: Then, in summary, there is plenty of evidence for quantitative deficiencies, but nothing conclusive or satisfactory for qualitative deficiencies?

GYORGY: Yes.

AUTRET: I think Dr Rao mentioned yesterday some evidence that methionine was completely missing in some milk. I do not know if it was mother's milk or cow's milk. That is rather surprising, as long as there is some albumin or casein left in the milk.

I think therefore we need more information on maternal milk, especially about the content in different proteins throughout lactation and also the quantity of milk secreted as long as lactation is continuing.

DEAN: To go on with the philosophy of supplementation, I think we may say that there is a high degree of success in the avoidance of kwashiorkor when milk is used, and a low degree of success when the supplements are starchy foods, such as cassava and arrowroot. This was clearly recognized by the middle of the nineteenth century, and it was derived directly from the division of foods into azotaceous—the nitrogen-containing foods—and calorifacient, the ones which did not contain nitrogen (18). It was quite clearly understood that the growing child would need the azotaceous foods and would run into difficulty when it did not get them (19). The concept was worked out by the Germans at the beginning of the century and they called the disease caused by lack of azotaceous foods, *Mehlnährschaden* (20); it is known in the French literature as *dystrophie des farineux* (21), and in the Italian paediatric literature as *distrofia di farine* (22). I think we must admit that we are all talking about the same thing, and that the condition has been recognized for a long time.

Much of that early work is difficult to understand because there was undoubtedly, at that time, a confusion of states of malnutrition arising from many different causes. I was reminded of that not only by our discussions here on V.O.D., but also by Professor Sénécal saying that two of his three hopelessly resistant cases were, in fact, fibrocystic disease. Fibrocystic disease was not described at the time when most of this early work was done, and quite obviously the records contain many different diseases in addition to cases that might be called kwashiorkor or *Mehlnährschaden*. But in spite of that, a special chain of events was clearly recognized.

You would have a gastro-intestinal upset in a child, which would be treated with a bland diet; then, when the bland diet had apparently been beneficial, there would be a premature resumption of the normal diet and a return of the gastro-intestinal upset. Then, the mother said, 'Oh, the other diet was so much better, we must go back to it.' They returned to the bland diet, and Czerny says, in his original description, 'This disease is very largely caused by the unwise physician.' He has allowed the mother to go on with this bland diet, and of course it is a very poor diet, and so you get the condition of *Mehlnährschaden* developing from it. That has been repeated several times, and now we have got to the stage where some French authors (23) have been able to report exactly the same chain of events, ending up by saying: 'Here we have, in Paris, kwashiorkor.' They did not use any other term; they did not say '*Dystrophie des farineux*'; they said, 'This is kwashiorkor.'

RAO: There appears to be a kwashiorkor-phobia all over the world now.

DEAN: It is possible, but I think they are telling the truth in this case. In Tunisia there was a rather interesting point made by Didier (24), that gastro-intestinal upset is common in late summer, and is usually treated by removing milk from the diet; then there is a high incidence of kwashiorkor. It all fits together, I think.

It was also recognized very early that various signs and symptoms might accompany the condition which was called '*Mehlnährschaden*'; these included what we can now recognize, I think, as scurvy, rickets, xerosis and keratomalacia. Professor Frontali has referred to the occurrence of those particular complications, especially keratomalacia and xerosis, in a recent publication (25).

WATERLOW: Rickets as well?

DEAN: Vitamin A deficiency principally, but he does mention rickets.

WATERLOW: The rickets I have seen—florid rickets—only develops in cases of kwashiorkor when they are treated.

DEAN: That is very reasonable, because if a child is not growing, it can't get rickets.

WATERLOW: Quite so.

AUTRET: In going over these old papers, we found reports of depigmentation that we missed the first time.

DEAN: Yes. I wasn't able to find that in the German literature, although Professor Frontali (26) has certainly reported it now.

Now, when lactation is failing, there is no doubt that the child, for many different reasons, is facing a very difficult time. I am sorry to go on with this series of platitudes, but it is intended to lead into the discussion of prevention. I think this difficulty is recognized in peculiar ways; for instance, by the fear of teething, which may or may not have a physiological basis, but may also have a superstitious basis. The teething period is also the time of transition of diet. The child, at that time, is needing to adapt itself to a foreign diet, with all that that implies. The withdrawal of human milk may possibly involve the withdrawal of protective substances in the milk. Professor Gyorgy may like to enlarge on this later.

The child at that time would normally be trying to grow very rapidly, more rapidly than at any other subsequent period in its life.

The child is also trying to develop in many ways. It is not only trying to achieve its chemical maturation, which I think is an extremely important concept, because it is directly related to nutrition; it is also developing mentally, as is shown by the enormously wide scatter that you get in tests which are intended to measure mental development in children between 1 and 3 years of age. Incidentally, that is the time too when there is an enormous scatter in the electroencephalogram, which presumably may have some relation to mental development.

Withdrawal of the breast, as many people have already pointed out, involves the loss of some measure of security, and the child is at that time increasing in its awareness of its surroundings and in its ability to explore them, and is being led by its greater abilities into a greater contact with the unknown. Also, to come down to a much more mundane subject, its mobility of course exposes it to increasing risks of infection and infestation.

All this is commonplace, but it is worth mentioning that there is, in many primitive communities, fear of the restricted amount of the life force available, and I think we can go further than that and say that the child that is thought to be damned is likely to be damned. As Dr Clements has already said, the removal of the baby from the mother may easily be the starting-point for the development of the kind of child described by Bowlby, the deprived child (27).

In fact, we have started some work which arose directly out of my description to Dr Hargreaves, of the Mental Section of W.H.O., of the condition that these children get into. He immediately said, 'Read this in Bowlby.' But it must be realized that we see children who have been deprived of maternal affection side by side with others in an apparently identical condition, who have not been deprived, at least of the presence of the mother.

CLEMENTS: I think that is very important; you have to differentiate between physical deprivation and spiritual deprivation. In some communities there are children who are being cared for apparently in a normal way by the mother, but who, in fact, are suffering spiritual deprivation. It is very difficult to detect. It is much more common, I should imagine, in the sophisticated, well-developed countries, than in the underdeveloped countries.

We have just had an international seminar on mental health in childhood, with representatives from about sixteen Asian and West Pacific countries. They endeavoured to correct the fallacy present in the minds of some of the people from better developed countries, by pointing out that in many underdeveloped communities a significant number of mothers do, in fact, submit their children to spiritual deprivation when, on the surface, they appear to be looking after them.

DEAN: At this stage there is no doubt that an increase in the plane of nutrition is required. It is no good going on as you were. You've got to increase the amount of food which is being given, and if that increase is not established, one way or another, the least thing that might happen is that weight gain becomes slower. It is possible too, that skeletal development may be retarded. Those are obvious effects that we can easily measure, but there are undoubtedly more subtle effects. I think there is some evidence to show that the processes which need nitrogen may fail first, and that sites of maximal enzymatic activity may be the first to be affected. We know that there is an early failure of enzyme activity in the gut; Veghelyi (28) says that in his cases lipase was the first to disappear, and then amylase, and that these enzymes were reduced in his cases of kwashiorkor before there was any detectable alteration in the serum proteins. Then, if you cannot digest your food—putting it as bluntly as possible—isn't it likely that anorexia will develop? I don't know which comes first and which comes second, but the two must, I think, be closely related.

When anorexia develops, the calorie intake falls; when that happens the result depends, at least to some extent, on the quality of the food that the child gets at that time. When the food has a low ratio of protein to carbohydrate it is conceivable that the tendency is towards the development of kwashiorkor. When there is a normal ratio of protein to carbohydrate, it seems reasonable that the child will be pushed into the state of marasmus rather than into kwashiorkor.

In the infant, with its very special needs for growth and development, the picture is likely to be confused. These important needs of growth, this azotaceous process, must influence the result, and so what starts as a pure calorie deficit produces an impure final picture. I think it would be surprising if marasmic states did not contain a large element of protein deficiency. I am saying this in an effort to reconcile my ideas with the suggestions that have been made that I was going too far in the wrong direction.

Rao: You are now going in the right direction.

Dean: I'm glad you think so. I think that the arrest of this process may be possible at any stage, if the diet is temporarily or permanently improved.

I have the impression that I have been pushing back further and further the last possible day on which I can produce a remission. We are gaining time as we gain in the efficacy of our treatment. The margin is small, I believe, between fair health and disease, and not very much is required to push the child further down or to raise it out of the downward track on which it is proceeding.

If the child is on the way downhill—and I think that this is probably true of a large proportion of the children in Uganda—its downward development may be accelerated by an infection, which may act in a number of ways. These effects have been demonstrated in normal children, and therefore might reasonably be expected to occur also in abnormal children. I won't go any further than that; I won't say that they will be worse in slightly malnourished children.

The food intake is further reduced by the infection. The child does not want to eat. If there is fever, catabolism is increased, and there is certainly, even in the normal child, a decreased utilization of food. That was shown very well by Veghelyi [illegible], who said that in various infections it was possible to demonstrate quite marked reductions in pancreatic activity in a normal child. What, then, happens to this abnormal child? Undoubtedly, the same thing; perhaps the same thing, but to a worse degree.

In addition to that, infection in the normal child will undoubtedly lower cellular metabolism in various ways. That is a vague phrase, but it is a fact that infections will produce, in a normal child, an alteration of the albumin-globulin ratio, just like that which has been described in cases of kwashiorkor ([illegible]). In the first session I made the point that I had abandoned the albumin-globulin ratio as a diagnostic criterion. However, in general, I am not convinced that malnutrition necessarily predisposes to infection. The evidence from animal experiments is certainly inconclusive, to say the least of it.

WATERLOW: Can you put all infections together like that? In the case of malaria I think there may be an important inter-relationship, judging by the experimental work I have read, and by my own clinical experience in the Gambia.

WILLIAMS: I agree.

GOPALAN: Rather than malnutrition predisposing to infection, it is often the other way about. I have already shown some evidence to suggest that gastro-intestinal infection seems to predispose to the development of kwashiorkor. On the other hand, we have not found any correlation between the incidence of kwashiorkor and the incidence of respiratory or non-alimentary infections; so it seems to me that the precipitating role of infection was not related to any metabolic effects of infection as such, but to the direct effects of intestinal infection on the alimentary tract, interfering with the absorption of food. It is quite possible, theoretically speaking, that infection of any type should predispose to the production of kwashiorkor, but in actual practice we have not found evidence of this.

DEAN: That is very interesting. I was interested also in Dr Rhodes's presentation, because her data, as it seemed to me, suggested that there wasn't a very close relation between malnutrition and infection. In our cases of hunger oedema in Germany we failed to demonstrate any large alteration in ability to produce antibodies as a result of undernutrition. That is the kind of thing that badly needs to be repeated in kwashiorkor; we want to know something about the actual ability to produce antibodies.

I have one piece of information about the effect of infections which is important. The children under treatment in my ward very seldom get cross-infections. They are, you may say, being protected by a high protein diet, but it is the rarity of infections and not their frequency which has impressed me, in the same way that it is the rarity rather than the frequency of sepsis in the severe skin lesions which is remarkable. I can think of nothing which should make a more perfect nidus for infection than those lesions, particularly the wet form. The fact is that they never seem to become septic.

McCulloch: Do you get cross-infections as a general rule in your hospitals in Uganda?

Dean: I think not so much as in Europe. If there is anything in the idea that cases of kwashiorkor are particularly lacking in resistance to infection, one might expect to see much evidence of infection at post-mortem, and that is not the case, in my limited experience.

Gopalan: Did I understand you to suggest, Dr Dean, that cases of kwashiorkor are more resistant to infection?

Dean: No, but in my experience they are not less resistant.

Gopalan: I think the suggestion has been thrown out by at least one other worker that cases of kwashiorkor are actually more resistant to infection, and I think the argument he advanced was that in these cases you find evidence of increased γ-globulin. I do not know if this reasoning is justified, but in my own experience I think that the susceptibility to infection is certainly as high in cases of kwashiorkor as in normal children. I have seen cases presenting the skin lesions with suppurative ulceration, and several others which died of broncho-pneumonia.

Dean: Oh, yes, that happens sometimes, but when you consider that almost every one of our severe cases has very bad ulcers, I would say it is the absence rather than the presence of much septic ulceration that is an outstanding feature.

Gopalan: I agree.

Peña Chavarria: On the other hand, in my experience infection of the skin develops faster and in a more florid way in cases that are undernourished.

Scrimshaw: But, as has already been pointed out, shouldn't one differentiate very sharply among diseases? There are certainly some diseases which are more frequent in cases of protein malnutrition and others which do not appear to be related at all, and probably others again where there is increased resistance.

Cruickshank: There is some evidence, which Dr Gopalan may confirm, that in certain virus infections the malnourished animal or human being is not nearly so susceptible as the healthy well-nourished one.

Bras: But against this, may I remind you of the statement of Professor Fernando that I quoted the other day, that the mortality in Ceylon from virus hepatitis is about a hundred times as high as in the United States and Europe.

Williams: There is much undernutrition in Ceylon.

Rhodes: Professor Fernando has studied the diet and points out that the more deficient it is in protein the greater are the mortality and complications from hepatitis.

SCRIMSHAW: Tuberculosis is a prominent example of a disease to which the undernourished person is more susceptible.

CRUICKSHANK: That has never been established, Dr Scrimshaw. There is a higher incidence of tuberculosis in the malnourished no doubt because of environmental factors, but there is no evidence of increased susceptibility as a result of malnutrition *per se*.

BURGESS: I think that Professor Keys, in his book *The Biology of Human Starvation* (31), summarized this evidence. I do not think he would quite agree with that. I think he concluded that there was both an increase in susceptibility and an increased rapidity in the course of the disease.

CRUICKSHANK: I think that we must differentiate between susceptibility and severity. Quite obviously an undernourished child, once infected, may very well go downhill and die much more rapidly. But it is a question; is that undernourished child more susceptible to infection? I think that Dr Dean was bringing out that point.

DEAN: Yes, that is the point; the spread of the disease is said to be very fast in an infected, undernourished person. But susceptibility is a different thing.

I shall end with two small points related to each other. As far as I can see, there is a danger that kwashiorkor may be moving into the towns. In Uganda the industrialization of the country is leading to larger and larger conglomerations of people. That is going to have a number of effects. There is no doubt that kwashiorkor is a disease of poverty, and it arises from the fact that good protein, like good food of every kind, is expensive.

I remember being struck, in Orr & Gilk's report (32) by the simple fact that people who couldn't know much about biological analyses were willing to pay about four times as much for what was obviously a good edible earth in northern Kenya than they would pay for a poor one. It seems that, almost instinctively, people are willing to pay more for good food, and that certainly applies to good protein. Dr Widdowson (33) found, in her study of children before the war, that the amount of protein in the diet, particularly animal protein, rose with the economic level of the parents. The result is, of course, that the protein tends to become less and less accessible to the people who need it most.

There is another point about this drift to the towns which I have been told has been proved in Hong Kong; the arrival of artificial milk seems to have coincided with a remarkable failure of breast feeding. If we allow that to happen unchecked in other parts of the world, as an inevitable concomitant of better facilities and increased civilization, I am afraid that kwashiorkor will certainly increase.

CLEMENTS: Dr Dean has made the point that kwashiorkor seems to go hand in hand with local poverty. I should like to throw in another feature for discussion and consideration later, and in this I carry the torch of my former colleague, Dr Hargreaves. Is it enough to consider food supply alone in this problem? The stories we have heard or read seem to indicate that much more than the provision or lack of food is important, and you cannot but be struck by the fact that many of the women whose children have protein malnutrition or some other form of malnutrition seem to be carrying a great many more burdens—emotional, social and economic—than the mothers of the children who do not suffer in this way. Is it right to look at this problem as one of food alone, without trying also to see the total background of the community? Here in Jamaica, for instance, you have a high percentage of social and, surely, of emotional insecurity in the rural population, so that many women do not know where their ultimate future is and what are the terms of their security.

An American social anthropologist, summing up the discussion in the seminar to which I referred a little while ago, said, 'Have these women got so many physical burdens and so many emotional burdens to carry and to work through, that they haven't anything left over to give to the care and nurture of their children?' (34). If the answer to that question is yes, then it is futile to push extra food at them, if they haven't got the resources in their own lives, and the spiritual capacity to make use of the material which you are providing. I suggest, therefore, that we must take into account the social background against which this disease occurs.

RAO: These social and emotional outbursts are, perhaps, appropriate in sophisticated countries, but as far as the so-called underdeveloped countries are concerned, it is a question first and foremost of food, of getting enough to eat, let alone enough protein. The calories come first; then, when there are at least enough calories to go round, comes the question of adequate protein; the third factor is lack of protein of animal origin. These, in that order, are the problems with which we are faced in the underdeveloped countries. To a certain extent, no doubt, you have to consider this against the social background, but I think that we should limit the question of protein malnutrition to the age period of about 1–3 years, with which we are now concerned.

SCRIMSHAW: I think, Dr Clements, that your point should be amplified by reference to the psychological factors involved in feeding programmes. I might recall the work of Widdowson (35) in an orphanage with a stern attendant, and also refer to our experience in a rural village in Guatemala. We introduced a milk programme, with considerable resistance from the community, who doubted whether it was proper food and claimed that it caused gastro-intestinal disturbances. During the first 9 months the rate of gain in height and weight was actually lower than in a control village (Table 17). The gain in height fell from 0·33 cm. per month to 0·24, and in weight from 0·17 kg. per month, to 0·13. It was not until the second 13-month period, when the programme had been accepted, that these rates came back to normal and showed a definite improvement with milk. In the second year a new group of children entered the school and were included in the feeding programme, and this second group responded immediately. During their first observation period their rates of increase in height and weight were nearly twice as high as in the children who 'broke the ice' with the programme (Table 17).

Table 17. *Effect of a milk-based protein snack on adjusted growth rates in Guatemala*

Group	Age*	No.*	Interval (months)	Ht. (cm.)	Wt. (kg.)	Interval (months)	Ht. (cm.)	Wt. (kg.)
				1950			1951	
1	9·1	28	9	0·24	0·13	13	0·42	0·24
2	8·1	26	—	—	—	13	0·45	0·24
3	8·1	27	—	—	—	—	—	—
				1952			Total	
1	9·1	28	6	0·34	0·21	28	0·33	0·19
2	8·1	26	6	0·40	0·19	19	0·42	0·22
3	8·1	27	6	0·40	0·24	6	0·40	0·24

Approximate M.S.D. for height = 0·14. Approximate M.S.D. for weight = 0·10.

* Average initial age and initial number.

McCulloch: Were they given the milk in school or was it given them to take home?

Scrimshaw: This was a supplement given in the schools. To some extent there was difficulty in getting them to accept it, and there were some irregularities in attendance, but the children took most of it.

My point is that in the first 8 or 9 months the results were poorer than if nothing at all had been done for them, but in the succeeding 2 years, when the community accepted the supplementary programme and believed in it, the results were very satisfactory.

Williams: I thoroughly agree with you. I think that the whole problem should be considered as one not merely of putting food into the children, but also of improving the attitude of the parents, and improving the mother's knowledge of what the child needs.

In the Gold Coast I was always impressed that there was plenty of money, and that only 1%, of the people, at the very most, could not afford to buy milk when they were advised to do so. The problem was to convince them that the milk was necessary. This was done by bringing the mother with the child into hospital and letting her see the effect.

Professor da Silva, a paediatrician in Ceylon, has seen a great deal of kwashiorkor (they call it 'rata' and 'mandama'—it is well recognized) and the toddler mortality is very large. He said that food deficiencies are not due so much to lack of money as to the wrong use of it in purchasing the wrong types of food and in using the wrong methods of cooking.

I feel that these two things are most important: the attitude of the parents, so that they pay attention to the child's needs, and secondly, that the parents should be taught how these needs can be met. But it is not only the attitude of the mother that has to be considered. Another thing, which has not been stressed enough, is that governments should organize the kind of system which will help in getting nutrition and general child care over to the population.

Santos: Protein malnutrition cannot be considered as an isolated problem; both it and undernutrition must be regarded as the consequence of many factors, of which the most important is the low economic and social condition of the population. This, I think, is the basic factor. We should not say that this is none of our business.

Somebody at this meeting said that a doctor who comes into the field of nutrition has to become a biochemist, a pathologist, and a clinician; I think he should also be a public health man, something of an agronomist, a sociologist, and an economist if he really wants to see his ideas and aims fulfilled, even taking the risk, as Dr Fremont-Smith pointed out, of knowing less and less about more and more. As a doctor dealing with the problem of nutrition he has to become the adviser of his government and its agencies, and to co-ordinate their efforts, for he is the one who knows the end results of undernourishment and hunger and their effect on health.

Therefore, going back to the priorities that we think should be given in the solution of this problem, we put social and economic conditions as the main and basic factor; to this basic factor, and often arising from it, we should add, secondly, ignorance. Third come the factors that we have been discussing this morning, environmental conditions like rainfall, hurricanes, temperature, geographical situation, poor soil, and so on. Fourthly, this problem is a consequence of lack of leadership and technical facilities and skills, and of the funds for improving those facilities. If you have poor soil or a bad geographical background, you cannot combat those without technical skill. Fifthly, are emotional and psychological factors, as Dr Clements pointed out, including what we might call lack of freedom, not only political freedom but also economic freedom.

Furthermore, we must consider protein malnutrition as a possible world problem, and promote a world consciousness of the problem. We should spread the idea that we are talking here in words that can be understood not only by clinicians but also by the whole population. We should not call this a tropical disease, because it is not. As Dr Dean said this morning, it is a disease of poverty and of underdeveloped areas. By giving priority to what we call a tropical disease, we give priority to environment, which we don't think holds true.

Clements: This takes us on to the subject of prevention. Would you like to open, Dr Dean?

Dean: In contrast to Dr Santos, I shall limit myself to details, mostly technical, of the way in which I think the problem can best be met of improving children's diets, particularly in regard to their protein content. It must not be thought that I deprecate the importance of these economic and social factors. It is enormous. But it so happens that the contribution that I can best make is of a more immediate—if you like, of a more parochial and technical—kind.

Almost the first thing we have to try to promote is the recognition of this disease at an early stage. I cannot define the early stages, and I came here hoping that other people would help me on this particular point. But there is no doubt that unless we can diagnose the state of 'a little bit of kwashiorkor', we shall not get very far towards its prevention. In those districts where kwashiorkor is likely to occur, everybody must be made familiar with it. The administrators and all those who come in contact with children, especially the school teachers, should have some instruction in what we think they should look for. And, of course, when it is possible to get at the mothers, as it is in some fortunate places where clinics are available, they must be told to watch for it.

Rao: We are considering the age group of 1–3 years, and I don't think that age group comes into contact with the school teacher.

Dean: I should have thought that his influence would go right through the family, if it were properly used.

Peña Chavarria: In Costa Rica there are clubs of fathers and teachers. I think Dr Dean's advice is wise, because the teachers may give the fathers instruction about children who are malnourished, even if they are not of school age.

Dean: I was thinking of the parents-teachers associations that exist in some places

Rao: I appreciate the idea, and I just wanted to have it clarified.

Clements: I wonder, Dr Dean, if you haven't withdrawn and retreated from the position you reached this morning, which was so ably taken up by Dr Aykroyd? You presented us with a picture of a fairly universal pattern of a low protein consumption throughout large areas of the world, and Dr Aykroyd said, 'Doesn't it seem that this is a much broader problem than just the identification of a specific disease?' It seems to me that you are retreating back to a specific disease and its early recognition and the endeavour to prevent it, whereas this morning the keynote of the discussion was that we must consider the broad problem of the need for better protein and more of it throughout very large areas of the world.

Dean: I am sorry if I have gone too far back. What I was going to say was intended to offer a line of educational approach at this particular level.

One of the first things that we must try to make known to people is this very simple thing—the value of breast feeding. The reason why at the beginning I dealt so much with breast milk and other milk, was really because there is no doubt that we have, from different places in the world, examples of failures of breast feeding which seem to result from encroaching civilization. Surely it is of importance to try to establish and to maintain an appreciation of the value of breast feeding. Isn't that basic to this problem?

The protection which is afforded by breast feeding must be considerable and, as the first part of our educational programme, I think we must do something about this particular point.

Santos: We don't think that breast feeding, at least as we have it in our country, is a problem for education. On the contrary, the more educated the family, the less the mother gives breast milk to the children. This is not because the mothers don't know or don't want to, but because they don't have any more milk. Therefore, I don't see how education, except in certain groups, could improve breast feeding.

Dean: I think you are using the word 'education' in a different sense from me. I am not referring to general education, but to education about this specific point—the importance of continuing breast feeding for as long as possible.

Williams: An experience that we had in prisoner-of-war camp is relevant to this. We had twenty babies born in camp; twenty babies were breast-fed, and twenty survived. They were all breast-fed for 1 year, although the mothers were European women who would not, under normal circumstances, have breast-fed their babies for more than 4 or 5 months. But we were an educated community and therefore we saved the best food for the pregnant and lactating women. The women were convinced that if their breasts gave out, then the child would have a poor chance of survival. Of those twenty women—I think nineteen were pure Europeans—none of them ceased lactating until the end of the year, and only then were the babies completely weaned from the breast.

Santos: Breast feeding is closely related to economic conditions. One of the reasons why the mother stops feeding the child is because she has no more milk, and the other is because she has to go to work. It is also an economic reason that makes for long breast feeding, because it is much less expensive to give the child the breast than to buy food.

Dean: I should have thought that was an argument in favour of encouraging people to breast feed. There are some groups, I think, who do need that encouragement.

I am looking at this as a very wide problem. Surely, one of the diseases of civilization is an inability to breast feed. I said this morning that I was afraid that kwashiorkor was going to move into the towns. Isn't it worth while our considering these points when we have already agreed that the maintenance of breast feeding is one of the ways in which we can prevent the onset of kwashiorkor?

Burgess: It is quite well recognized that in some areas social custom or improvement in social standing coincides with a decrease of breast feeding. Certain people in the country in which we worked—Dr Williams will back me up here—felt that one of the risks of wide-scale milk distribution is that it does reduce breast feeding.

Williams: Among the Chinese the poorer people will breast feed, but not the fashionable ones. They bind their breasts from early childhood, and it is supposed to be rather an animal function to breast feed your babies.

I agree that the encouragement of breast feeding is most important. It is a question of orientation and attitude.

Dean: The next point on which education is needed is to emphasize the special needs of the child at weaning, and the unsuitability of using an unmodified adult diet at that time.

Santos: The reason why they use the unmodified adult diet is that they don't have money to buy baby foods, which are expensive in the less developed countries. I think it is a matter of increasing the industrial production of food at lower prices.

Rao: But our job is not to encourage the mothers to buy baby foods, but to utilize the cheap foods which are locally available and which can still prevent the condition, but which at present they do not use.

Santos: It is not easy to have staple foods available which are good from a preventive point of view.

Rao: That is what we've got to find out.

Gopalan: In our experience, in these poor communities there is generally no qualitative difference between the diets of adults and of children of the post-weaning age. Both are defective in quality, but there is this important difference: while the adults' diets are fairly adequate in calories, the children's are deficient in calories. I think that could be avoided if the idea were sufficiently inculcated in the minds of the parents that the children should get the highest priority. The distribution of the available foods within the family is not as rational as it might be.

SANTOS: I think that is a very important point.

DEAN: Dr Gopalan has stated that point much better than I myself would have done. The third point about education is that in some places it is necessary to set to work deliberately to break down the superstition about the unborn child harming the child that is coming.

Leaving aside theoretical considerations, the practical problem is to find ways of improving the diets of children at the weaning stage, and I think there are two possible ways to be considered. The first is by food grown in the village and processed at home in such a way as to make it suitable for the child; the second is the provision of food which is already processed and that can be added to the diets of children at the age when they are most susceptible. I don't mean by that the provision of baby foods in expensive tins, but I hope to show that there may be some other way of providing good food.

Education, if it is to be worth anything, must have the practical application of its tenets very near at hand and at heart, and I think it would be absolutely fatal to stimulate a demand that could not be satisfied. That is why I put education first. If you are going to educate, make sure that there is something to follow up the education with; it isn't much help to mothers to tell them that their children would be much better if they had food that isn't available to them. Therefore the practical programme must not lag behind, and practical possibilities must be kept well in mind wherever the educational programme is leading. I am sorry to put forward something that you know already, but there may be some people who do not realize the importance of this.

SCRIMSHAW: I think there are many cases where that principle has not been taken into consideration in feeding programmes, so it does need stating and re-stating clearly and firmly.

DEAN: It is fatal, therefore, to satisfy a demand for a short time, without understanding exactly what is going to happen when that demand can no longer be satisfied.

SCRIMSHAW: Don't say 'demand'; say 'need'.

DEAN: Well, if you like, need, but you have stimulated a demand. The distribution of dried milk falls, of course, into that category.

There are two further principles that I want to enunciate. The first is that in this kind of programme, all the foods which are used must be grown very near to the places where they are to be consumed. A programme like this cannot afford any extra burden of cost for importation. You must make use of those foods that are available, even if it means making foods available which were not so before.

Another principle is that the direct utilization of food must be encouraged, and any processing that can be avoided must be avoided. The direct utilization of food is an important point which is sometimes not appreciated. If you put food through a domestic animal such as the cow, you get back, if you are lucky, about a tenth of what you put in. When I talk about direct utilization of food, I mean that we should try to cut out this intermediate step, this processing. The cow is a very good piece of processing equipment, but looking at this as a world problem, a domestic animal is a very expensive device for food. Admittedly we all like to eat animal protein, but the fact is that we must adhere wherever possible to this principle of the direct utilization instead of the second- or third-hand utilization of food.

AUTRET: That is only true when there is land competition between the human population and the cattle population, and as long as the cow is consuming something which can be used directly for human consumption.

DEAN: But very little of the food which is used by the cow need be used by the cow; in theory, and to some extent in practice, it is possible even now for us to take the food from the cow and give it to the child.

AUTRET: Part of it, yes.

DEAN: I don't see why you say 'part of it'.

SCRIMSHAW: As Dr Autret has pointed out, there are a number of things that are not suitable for human consumption, but which can be processed through the cow.

DEAN: That is a theory which, I think, will have to be broken down.

CRUICKSHANK: I think we are distracting Dr Dean from a very useful point that he is making.

AYKROYD: Let him state the case, and F.A.O. will have a word on that a little later.

DEAN: This, I think, is a basic principle: as long as you are wasting nine-tenths of your food, which I think could be used directly, or of which a very large part could be used directly, you are doing a disservice to man.

CLEMENTS: That is a hypothesis which you are putting up, which the meeting will have a chance to discuss later.

DEAN: You can call it a hypothesis, but it is supported by actual figures of what you get back for what you put in.

MACKAY: Can we have those figures?

DEAN: You can find them in any manual on the utilization of foodstuffs by domestic animals.

Clements: That is only part of the hypothesis. Will you proceed, Dr Dean?

Dean: There used to be some justification, I think, for the old-fashioned approach of the physiologist who divided proteins into first- and second-class. But I think it is true to say that in recent years the differences between first- and second-class proteins—that is, between animal proteins and plant proteins—are tending to be reduced. It seems to me not hypothetical, but a very reasonable statement of the way in which events should be shaped in the future, to say quite categorically that unless we can make the division between first- and second-class proteins even smaller than it is now, this world is going to be short of a number of very useful protein foods. The world might be able to supply itself with plant proteins, but I don't think it can afford, in these times, to supply itself with animal proteins. That, of course, is an exaggeration, but I think it is a basic principle worth considering. The difference between first- and second-class proteins depends, as has long been known, on differences in amino-acid content. Now we have a more exact knowledge of the deficiencies of one class of food compared with another, and a better knowledge of how we can make up for those deficiencies.

I would not have gone so far as I have except under provocation, but I would say that the principle of using domestic animals for the production of food is bad. It may, however, be possible to use some animal products which are at present wasted. For instance, in our local fishing industry it has for a long time been impossible to get hold of any scraps of fish, because it is an African characteristic to eat absolutely everything of the fish, and I think that some of those odd pieces of animal protein which do not usually come into human consumption must be considered as possible and useful sources of protein.

The fisheries in Uganda are a good example of what can be done. We have in the west of Uganda a series of lakes which have recently been utilized for a fishing or fish-collecting industry. Quite recently it has been realized by those in charge that it is wasteful to transport the heads and tails of the fish all the way across Uganda. They have now decided that it would be more economical to fillet the fish and to leave the heads and tails and offal behind. The Agricultural Department and the Animal Health Department, with whom we work closely, became interested in the possibility of making fish meal from those waste products, and now we have the beginnings of an industry which we hope will be able to provide some edible material from them. Samples which I brought back to England when I came from Uganda are now being analysed.

We shall, of course, go on and see what we can do with these fish meals in the feeding of children. We have the kind of organization where that can be tried under controlled conditions, first of all with very small groups of children and with animals, and later more extensively, if the first results seem satisfactory.

I have for a long time been wanting to find out what has been done on a similar scale, in a similar way, in other parts of the world. I believe Dr Vergara knows about the trials which are being made of fishmeal produced by the South African fishing industry.

VERGARA: Yes, we have been trying in F.A.O. to experiment with two different samples of fish meal, one produced in South Africa, and the other one in the United States. So far, we are only at the preliminary stage.

We have a group of 140 school children from about 7 to 14 years of age, who receive every day 90 g. of bread with 10% fish flour. They eat the bread as part of their lunch. We switched them, without letting them know, from the customary white wheat bread to that containing fish flour. Up to the time when I left Santiago 2 weeks ago, we had given them the bread for 3 weeks and it had been perfectly accepted without any complaints at all.

We hope that fish flour can be incorporated into wheat bread as a possible solution to the protein problem, especially in Chile, where the main staple food is wheat bread. Chile also has a long coast-line where more productive fisheries can be developed. At present a certain amount of fish meal is being produced for animal feeding. It is hoped that, with the help of U.N.I.C.E.F., a small-scale plant for processing fish flour for human consumption can be established. This would encourage industrial production of fish meal to be mixed with part of the wheat flour consumed in the country. The fish meal could probably also go into mixtures for child feeding. The young children in Chile are fed on a kind of gruel made of toasted wheat flour, and if we could get some fish meal into this, it would be an important step towards improving child nutrition throughout the country.

CLEMENTS: How much extra protein do these school children get as a result of this regimen?

VERGARA: The protein content of the fish flour, according to the chemical analysis made by the South African company, is about 70%, so that in each piece of bread they get from the fish flour about 7 g. of protein and about 500 mg. of calcium, and a certain amount of vitamin B_{12}—we do not yet know how much. We are also experimenting with various dishes, but that is a very slow process. We have found so far that in one helping a child can take 5–10 g. of fish flour without any difficulty. It is quite acceptable. The sample that we got from the United States has a rather strong fishy flavour, whereas the sample from South Africa has almost none; in fact, when we incorporate the South African fish flour into the bread it is very difficult to detect any flavour of fish. With the American sample the fishy taste may not be objectionable, but we may have to experiment with dishes over a long period, to be sure that people do not get tired of it.

This fish flour experiment is being carried out with the help of the Chilean Government, which is very enthusiastic about the results we are getting and is considering a big programme for incorporating fish flour in wheat bread.

BRAS: What part of the fish was utilized for this? Is it the normal edible part, or the offal, which is usually not used?

VERGARA: I couldn't tell you for certain, but I understand that it is the whole fish that is used, since the calcium content of the fish flour is rather high. The chemical analysis made by the Chilean laboratories shows that the fat content is very low, a fact that of course makes the product easy to preserve. We have a sample that had been kept for two years before being sent to us, and it is in perfectly good condition.

AYKROYD: I should like the group to understand that this whole project is very much in the initial stage.

VERGARA: When I left Santiago 3 weeks ago, the bread experiment had been on for 3 weeks. We expect to continue it for 4 weeks more and then to make some further tests with a kind of hard bread called 'galleta' used daily in the rural areas of the country.

DEAN: I think that Dr Autret has some information about fish, which I should like to hear.

AUTRET: I am not going to discuss the entire question of animal protein production. Every one knows that fish is a good source of animal protein, which has not yet been correctly exploited. There is a possibility of increasing the supplies of fish, but that is a slow process which requires much material and training. I am not going into that problem here. One possibility is the development of fish ponds, in order to encourage direct production of food by the poor people among whom kwashiorkor occurs. That is our main problem, on which F.A.O. has been working very hard. Fish culture has been developed in the Caribbean, in Haiti, for example. In Africa, the Belgian Congo and the French Cameroons are making a great effort. As an example, I shall quote one area of the Cameroons, where there are 83,000 inhabitants, and in 3 years 3500 fish ponds were built, producing 350 tons of fish annually. But, apart from increasing fish supplies, there is the possibility of using the tremendous quantities of waste products or by-products of the fish industry which go into fodder or even manure. Here we reach the point that Dr Dean mentioned. Part of these fish flours used up to now for animal feeding might be processed, with a very slight increase in cost, to make them suitable for human consumption. That is what we are trying to do now, with the help of various companies. Experiments have been started in Chile, in South Africa, in Senegal and the Cameroons. Seven to ten grams of animal protein are introduced under that form into the child's diet, but up to now the trials are being done only on children of school age. The question I would like to put to you is: how early can we give a good fish flour to younger children of the kwashiorkor age group? Can we give it even before 1 year old?

DEAN: This brings in several rather important points. I should like to congratulate Dr Vergara on his experiment. He also mentioned the extremely important detail that he is putting this fish meal into wheat bread. Many people right out in the bush or in more or less inaccessible places do buy a lot of wheat flour. It was astonishing to me to find that in the coastal district around Mombasa, the thing which was sold most in the local shops was wheat flour. It seems to be a food that people get a taste for very quickly. The addition of fish to wheat flour provides a means by which the smallest children can get some protein, because there is no doubt that young children do get gruels made of this flour. But I should like to know, and this is important, whether this fish meal has been tested under biological conditions.

AUTRET: That is being done now in South Africa.

AYKROYD: Do you think a very elaborate series of biological experiments would be needed to prove the value of a fish flour preparation?

MCCULLOCH: Fish meal is not a new product, and has been much investigated in animal nutrition.

DEAN: But I am not satisfied with experiments done 25 years ago on other products in other places. Before giving such a food to children, it must, as a matter of routine, be thoroughly tested.

GYORGY: You don't know what this fish meal is undergoing during the processing.

CLEMENTS: Could F.A.O. tell us what is the fish meal they are giving? Is it the whole fish, or a waste product?

AUTRET: The one tested in Chile is a by-product of the oil industry. This is a point we have to take into account in order to get the flour at a low cost. It consists of the whole powdered fish after the oil has been removed.

AYKROYD: What Dr Dean says undoubtedly applies to some of the vegetable products, but surely he is overestimating the need for proving that fish is fish.

DEAN: I don't think so, because many of these fish products which have been used in animal feeding contain the guts of animals that are bottom feeders, and these guts contain things like sand, which would not hurt a cow but might well hurt a child.

The principle must be accepted that if you are going to give a food of this kind to children, that food must be given a clean and complete 'run-around' in a properly qualified biological testing station. There is no way round that. First it should be analysed as fully as possible, for protein, fat, amino acids and minerals. Secondly, it should undergo a series of animal feeding trials to determine its toxicity, its biological value, and its value in supplementing poor diets. Lastly, it should be given a careful series of trials in humans, starting with adults and older children, then going on to younger children and finally babies. Sand and certain fats may not be toxic to pigs or rats, but they do upset infants. Sugars can be very upsetting. That is what we have done with new foods, except for measurement of the amino acids, which we are only now beginning to estimate, and that is what should be done for every new food.

Gyorgy: I fully agree with Dr Dean. Any new preparation destined for wide general use should be pretested on animals, infants, older children, and perhaps even adults. Assays on animals should precede those on human beings. Apart from the points Dr Dean has mentioned, the assay should include study of 'shelf-life', spoilage in storage, effects of temperature and humidity, etc.

Clements: I remember some years ago in Geneva raising with Dr Williams the question of using some of the fish meal products that were common in the East in feeding young infants. She said that they were not strictly processed, and pointed out that the moment you start using these fish foods the infants develop gastro-intestinal disturbances. I know they are not comparable, but I wonder to what extent the experience with raw products of this kind can be applied to our present problem. Dr Vergara has asked, when will you give us the green light to go ahead and give this fish flour to young children? That is the point at issue. I think we have already carried out some tests with the older age groups, and it is the younger age groups that we need tests on now. I wonder if anybody in this group is ready to go ahead and say that you can feed this fish meal to 6-month-old babies, without any further biological testing?

Vergara: I should like to emphasize that the present experiments are being done only on school children. The possibility of their being extended to small babies is a thing to be considered for the future.

Autret: We have never claimed that experiments on older children should enable us to dispense with trials on infants. But we think it logical to begin with the older children, because we must first be certain that the product is well tolerated and does not cause digestive disturbance in these older children. Moreover, school children, and adults as well, are interesting in their own right. If one is going to introduce a product like fish flour it must please everybody, old and young, if it is going to find a place in the family diet.

If this first phase is successful, we come on to the second stage—trials in young children and infants. There, taste and smell are less important. The object of the trials is to determine nutritive value and digestibility. We have already initiated tests of this kind under the control of a paediatrician, and the experimental protocols are at the moment under discussion.

Animal experiments are necessary, but can take place simultaneously with the trials on older children. They cannot, however, replace the tests that have to be done both on children and on infants.

AYKROYD: I don't think it is a bad start. It is a biological test that Dr Vergara is conducting, which will move down the age groups in due course.

SCRIMSHAW: Is the plant already approved or under construction in Chile?

VERGARA: No, the situation is this: we want to find out several facts before we think about encouraging any industrial production of fish flour for human consumption. For one thing, we have to make tests to know whether people like it. As we say in Spanish, we have to have the horse before we can saddle it. I imagine that the programme for using fish flour could be started only after we have come to the conclusion that it is acceptable and its production feasible.

DEAN: I am delighted to return from this diversion, into a discussion of what we can do with plant proteins. My philosophy is that we have to make the best possible use of plant proteins, and this, in turn, resolves itself into making the best use of foods which are already available in a community, or encouraging the growing of crops for their supplementary value, or, finally, finding new sources of plant proteins. I shall go briefly through those in that order.

Under the heading of making the best use of foods already available, I think that is mainly an educational problem. It is extremely difficult to change food habits. I think that hardly anybody in underdeveloped countries cooks separately for children. That point came up in the last session. The only practical method is to suggest to the mothers that the children's part of the food should have some addition made to it. I think it would be completely hopeless to say to a mother: 'Stop giving that food, the food to which you are accustomed, the food you are brought up to, and substitute this for it.' The approach should be to add something to the child's diet. That seems psychologically much more sound. You are used to the food you always eat—I am, myself. Anybody who comes to me and says, 'You must stop eating that and substitute something else for it', will, of course, come up against opposition. But if he says, 'Your child will be better, I think, if you stick to your original way of life, but add this at a particular time', there might be more hope of acceptance. Most diets on which protein malnutrition occurs would benefit by being supplemented in this way, rather than by changing the basic staple.

Santos: That is the way we are approaching this problem in Brazil.

Aykroyd: That is much the best technique of nutrition education.

Dean: The next question is the possibility of processing foods in local centres, and distributing or, perhaps, selling the products. I myself think that sale is probably better than free distribution. A psychological factor enters in, so that usually something which is bought is thought to be more valuable and therefore *is* more valuable.

This process may cut straight across rural tradition, because certainly in my part of Africa food is very seldom bought. But the concentration of populations in urban areas, which I mentioned this morning as being liable to create local centres of kwashiorkor, brings with it a dependence on bought foods. We must consider this as one of the ways in which we can get food to the people who need it. The concentration of populations in this way does at least simplify the problems of distribution.

It is not usually possible to arrange for the processing in local centres of soya beans, but this difficulty has been solved in some parts of the world. Dr Burgess knows much more about it than I do. I am referring to the use of fungi for hydrolysing soya. But I cannot see myself being allowed to introduce such processes into any rural African community that I know of within a reasonable time, even if I could get the fungus to grow, which at the moment I have not been able to do. The other methods which have been used, by the Chinese particularly, for making soya available for human consumption (which is what it amounts to) would need a great deal of education before they were widely adopted.

Santos: We have been using soya flour in our bread, mixed with wheat flour at a level of 3%. This is soya flour produced in Brazil.

Dean: We might now consider the desirable properties of a processed food. It must, obviously, be a rich source of protein, because what we are trying to supply is in fact a protein concentrate. It has to be extremely cheap if it is to be sold. It must be acceptable, not only to the child but probably to all members of the family as well. It doesn't seem to be much good making a food which is not wanted by everybody, and I think there is more chance of a food getting to the children if everybody else wants to have it as well. I can see disadvantages but I can also see advantages in a food of that kind.

AYKROYD: Why shouldn't you have an emphasis on special foods for a special age group?

DEAN: A large-scale programme of this kind should be aimed at benefiting the health of the entire population. You may have to concentrate for a time on the children, but why not have something which is equally acceptable throughout the population? After all, protein malnutrition occurs in adults as well as in children.

I am sorry to go back to principles and not get down to facts, but, in general, it seems to me best to aim at making a food which represents its plant source as completely as possible. The selection of a fraction of the plant needs some special justification. After all, it is the selection of the starchy part of a plant that causes trouble in many instances. If we could eat the whole plant, with the stalks and the leaves and the roots and everything, we should get a much better mixture. We must consider, for instance, whether it is justifiable to make plant protein milks merely by removing the most easily soluble proteins, when you could possibly use the whole of the bean or the whole of the plant from which the milk is made. I know that 'milk' has a magic significance. Let us try to forget that and think of it in terms of what it actually supplies!

CLEMENTS: Will the rest of the world let us do that?

AYKROYD: There is something about milk.

DEAN: There is something about milk, yes. I am trying to find out what it is. Other people should be working on it, too; they shouldn't be working to try to find milk substitutes, though.

Beans, of course, are a very obvious source that we might use for this purpose—not only the soya bean, but also other beans. Nearly all of them contain between 20 and 40% of protein on a dry-weight basis. That is the chief reason why we should, perhaps, concentrate on beans. Some beans also contain a very large amount of fat. I would like your opinion on this, but my view is that children in places where kwashiorkor is found certainly do not need fat as much as they need protein, and if we have to omit anything from the diet, we could most reasonably omit fat.

It is possible that you can omit a good deal of fat from the child's diet without causing it any harm. As far as I can see, that is about all you should do to the beans, if you want to make the best possible use of them. But I think that a good case might be made for taking the fat from the beans and using it, partly at least, to pay for the cost of processing to render the residue suitable for children.

My own experience with soya milk production showed me that it was quite easy to lose a large part of the potentially nutritive material just by concentrating on solubility, and I remind you again that we are here involved with another of these conversion factors. You put food through an animal and get a small return from it. Equally you might be putting soya or some other plant through a factory and getting a small return from that. I know that in some circumstances it might be justifiable, but I ask you to consider whether it is absolutely necessary before you pay too much attention to schemes of that kind.

In this matter of preparing foods for children, there are a great many technical matters involved, and I can't possibly go into all those now.

These processes have been worked out in part but not fully. My own approach, which is considered in some circles to be far too leisurely, is to go very gently towards the pilot stage of anything of this kind, because I have had unfortunate experience of the amount of wastage that occurred when the manufacturing schemes were not very carefully controlled. I have particularly in mind the production of quite a large quantity—several tons—of a soya food which I thought was perfect and which gave, on biochemical analysis, a perfect answer; yet it completely failed to support the growth of rats because it had been spoiled in the processing in a new way which we did not appreciate at that time.

I have already mentioned elsewhere the way in which we are contemplating going toward the pilot stage, and I won't go into that now. We have in view, also, the possibility of using some big Indian-owned estates, where there are feeding problems in fairly large populations of African children. There we can make field trials after we have done all the routine preliminary trials with animals, which I think are so necessary.

The acceptability of a food is very important; it could easily happen that a plant is put up and a marvellous food produced, which is absolutely perfect in every way except that for one reason or another people will not eat it. It is worth going a long way to make sure the food is going to be acceptable before you go very far with your processing plants. That, however, may be an old-fashioned idea.

The next question is one which Dr Santos has already raised and in which I can see many difficulties—the question of alterations in village agronomy. The trouble is, I think, that the agricultural economy of a village is usually fixed empirically as a matter of long practice, and therefore, in the course of time, and after much trial and error, many people have come near to a reasonable utilization of their land. Changes are often extremely difficult to establish in a community which has a limited amount of land and where that land is devoted by tradition to certain purposes. For ecological reasons, too, there may be severe objections to disturbing the balance of an agricultural community.

Again, I would warn you about the dangers of schemes that have not been considered fully in their widest implications. I have had experience of one or two of those. I have seen the introduction of cassava as a famine crop in a district which previously did not have cassava. But cassava is a very easy crop, and it became a staple. For the first time kwashiorkor has appeared in that area where cassava is now grown and used, not only as a famine crop, but also as a staple.

But I think that something can be done. It has been possible to extend the use of beans, or at least the planting of beans, in a number of places. In this same district, where it looks as though the rural economy is going to be altered by cassava, sunflower has been taken on as a local crop; it is grown and processed at home, in the most laborious way, but I think it is an extremely valuable addition to the local diet.

CLEMENTS: When you mentioned beans, did you mean beans in general or soya?

DEAN: I mean beans in general. We have many different sorts of beans in Uganda.

SCRIMSHAW: I would like to make a point in connexion with the use of beans and also of corn; there are tremendous variations in the protein quality of corn and relatively large variations in the protein quality of beans. As an example, in a small village in Guatemala, several varieties of corn were grown, containing between 7 and 8% protein, which by rat-feeding trials was found to be of very poor biological value (36). By contrast, twenty of the best varieties of corn grown in the district gave an average protein content of nearly 10% (37); moreover, the protein of the varieties best adapted for growth in this particular village had a very much higher biological value than the protein of the corn actually grown (38). When a population is consuming 70% of its protein in the form of corn, changes of that sort have great practical significance, and there is reason to believe that much the same thing applies in the case of beans. (Unpublished data of I.N.C.A.P.)

DEAN: That is very valuable. I would like to go on now to the question of the search for new sources of protein. For this, the guide that we have found best to use is our local animal feeding industry.

The Animal Health Department of Uganda has a research department where we can co-operate in biological experiments. We take the view that both of us have the same basic problem. The cows and the other stock animals in Uganda are short of protein. They don't get kwashiorkor, as far as I know, but simply by improving the protein in the diet and doing nothing else at all, without improving the breed, it has been possible very greatly to increase the yield of those animals.

Among the foodstuffs which have been used for animal feeding there are, of course, many oil cakes, which are usually the residue of oily seeds after the oil has been pressed out or extracted in other ways. Of these, we have available in our own country soya bean, sunflower seed, groundnuts, cotton seed and linseed, all of them in large quantities, and they are capable of being used for animal feeding. I don't know why we shouldn't consider them also as being potential sources of human food.

Rao: Do you make use of groundnut flour?

Dean: Yes. We have just bought several tons of it. We find that when there is a local surplus of groundnuts, which are very much liked, some of the local manufacturers press out the oil, and then try to sell the residue.

Santos: Dr Dean, I should like to support your point of view, and emphasize the importance in underdeveloped areas of using those by-products that often are wasted. They can bring about much improvement in human as well as in animal food. For instance, we have cotton seed. The oil is taken out, and sometimes the residue is used for animal feed and sometimes for human consumption. We also have soya beans and groundnuts and many other things that are by-products and are thrown away because they don't have the necessary properties for animal feeding, or, perhaps, for human consumption.

Scrimshaw: I don't think these oil meals are wasted. They are exceedingly valuable, as Dr Dean has pointed out, in animal feeds. The question is whether any of them are applicable to human feeding. In Central America, for instance, we can use sesame oil meal as the basis for an all-vegetable ration, which produces maximum weight in hens only a little more slowly than a ration containing blood meal or animal products. It is therefore obviously a good protein source, and presumably could be used for child feeding, but as far as we know nobody has yet tried it.

Rao: We have tried using what we call groundnut cake flour. As you know, we are facing a food crisis, and there is competition between man and animal. The groundnut oil is expressed in the oil mills and the cake is used as a manure. The idea occurred to us, why not utilize this cake for human feeding? A special type of groundnut has been selected and carefully expressed twice so that most of the oil is removed, and a very fine flour has been made which we incorporate in wheat flour. This mixture has been used quite successfully, at a level of about 10%.

This has been tried mostly in adults; it was quite acceptable, and there were no unpleasant reactions. We have had no experience with it yet in children.

Clements: Has anyone else had any experience of feeding groundnut meal to children?

McCulloch: In southern Nigeria we used the groundnut meal with banana as a substitute for milk in those tribes where milk was taboo. We have been doing that for 20 years.

Clements: With satisfactory results?

McCulloch: Very satisfactory.

Dean: Did you add any calcium?

McCulloch: At that time, no.

Dean: That has been the trouble with groundnut, hasn't it, Dr Rao, in some of the Indian work? When you add calcium, you nearly always precipitate the protein, which is held to be a disadvantage. I don't see why it should be. I don't think anyone has tried using the precipitated protein. They always try to get it into suspension again.

Rao: The only disadvantage is that the groundnut flour still contains about 8 or 9% of fat, with the result that it cannot be stored for long. More recently we have had some samples of this groundnut cake flour, which were solvent-extracted, so that they contained less than 1% of fat. That is quite a good preparation and perhaps worth a trial in children.

For the information of Dr Dean, biological experiments of the type which he has been describing have been carried out on this oil-cake. When these cakes are fed to rats on a poor rice diet, they grow quite well. Therefore there is no doubt that they are nutritionally quite sound, and that it is a practical proposition to use this groundnut flour, particularly the type which is completely defatted.

Dean: I was put on to the idea of using groundnut flour by the discovery of a large surplus which we could buy extremely cheaply; in fact, I think it must be by far the cheapest source of protein available in Africa. It costs us a shilling for a pound of protein, which is astoundingly good, and it is not at all a bad protein.

Autret: Was it meant for human consumption?

Dean: No.

Autret: If it is to be used for human feeding it has to be specially processed, which involves a lot of work and extra cost. We have now interested a firm in northern Nigeria, where they are producing groundnut flour suitable for human consumption, but the price is much higher than yours.

Dean: This flour is at present being given to the children of a school. I have bought three tons of it, with the idea of going on with all the trials that I have already described and that I consider so necessary. The husks have been taken out, and the flour seems to be quite acceptable. We, of course, ate it ourselves and found it quite suitable.

György: You are already feeding it to the children. Did you have any biological tests made of it, Dr Dean?

Rao: We have done it in India!

Dean: Yes, we fed it to groups of rats, at levels of 100 and 50%, of the diet, and without adding vitamin B_{12}.

Gyorgy: For how long?

Dean: Only for 3 weeks, I am afraid.

Rao: How do you use the groundnut meal?

Dean: At the moment it is merely being made into a sauce to help get down the maize, in a school where the maize is being thrown away uneaten.

Scrimshaw: We have used large quantities of groundnut meal in 'atoles' or corn gruels, and found it well accepted by the children.

Clements: How about sesame?

Rao: Sesame is not used, unfortunately, on such a large scale in India as groundnut meal, except that part of the flour is used in the cooking of what we call curries. These are vegetable preparations, to which sesame cake can be added.

Clements: But you have had no experience in infant feeding?

Rao: No, it is not given to infants.

McCulloch: The Munshi tribe in Nigeria grow sesame; they usually parch it, and give it to children who have teeth. When I did a survey of these children, I was amazed at the lack of dental caries. I found that the limiting factor in the growth of the Munshi children was iodine; we fed them iodine, and produced children in 4 years who were on the average about 4 inches taller than their parents.

Santos: In Brazil we have also been studying new sources of protein, including nuts like the Brazil nut, which is a very common food in the Amazon area. We have hopes that this will be suitable, because it is a native tree and a food product in good supply. We are thinking of using this rich protein food to improve the diet of the people in the Amazon valley.

Dean: No doubt you know, Dr Santos, that the Brazil nut contains 3 times as much methionine, I believe, as any other nut that has been found. It would be wonderful if you could use that.

Santos: We call it 'vegetable meat'.

Dean: I would just like to mention yeast. Here is a substance which is full of protein and which no one has yet been able to use for its protein. That is a subject for research. We know quite well that if we try to give more than 30 or 40 g. of yeast to an adult it is liable to cause diarrhoea. We don't know why, and nobody seems to take much interest in the problem. It is a technical problem which could be tackled and should be tackled by those who are interested in reviving a plant costing many thousands of pounds, which is lying here derelict on this island.

Gyorgy: Yeast protein is very low in sulphur-containing amino acids, and it has been shown that to produce hepatic necrosis you have to give yeast protein.

Rao: We get cirrhosis in rats fed on yeast.

Dean: But you don't have to rule it out for that reason. It surely has potential value for supplementary feeding.

Gyorgy: But it is not so easy to supplement a food which is already low in sulphur-containing amino acids.

Dean: Could it not be supplemented with Brazil nuts?

Santos: What experience have you had with a combination of flours?

Dean: I have described my experience in a report that I wrote for the Medical Research Council on the subject of protein supplementation (39).

Autret: Did you give as much as 30 g. of yeast a day to your children, Dr Dean? How much can you give without causing diarrhoea?

Dean: I have given children with kwashiorkor up to 10 g. a day and had no trouble from diarrhoea, but I was using it as a source of B vitamins and not as a source of protein. I have never given as much as 30 g.

Another source of protein of potential value is the leaf proteins, which are much more complete, on the whole, than the partial proteins that we habitually use. But they are also an excellent example of the difficulties in large-scale use. Not long ago I was discussing these difficulties with Dr Pirie of the Rothamsted Research Station. He can make quite good food material from leaves on a small scale in his laboratory. The trouble comes when he tries to translate such a thing as a simple kitchen mincer into a plant which will produce several tons of crushed material a day. The technical problems there are not only the removal of the fibre, but also the concentration and stabilization of the protein. At present all these processes are costly and difficult, but they are still probably much cheaper than giving the same plants to animals.

Aykroyd: I must take issue with you on that point. I don't think you are presenting it in quite the right light.

Dean: I am only entering a plea for research on all these possibilities, but with full biological control of the end products. I know quite well that elementary analysis won't tell you very much, and you have to go through the whole range of animal and child-feeding experiments before you are justified in going on to manufacture on a laboratory and pilot-plant scale. As Dr Santos has said, it is necessary to try to keep all these things in hand at the same time and to have people who are willing to look at this problem from the point of view of the food production of the country and the processing of foods and the feeding of children.

Perhaps I should make a brief summary. First I think that a certain amount of education is required.

Secondly, I have talked at length about the processing of foods that can be added to existing diets; however, much knowledge of the effects of processing is required, not all of which is immediately available. I must repeat that we should not go into full-scale production until the preliminary work has been done soundly. In all stages, biological control must be maintained.

Finally, I want to come back for one minute to the question which was raised by Dr Clements this morning. This is a social problem. We must never lose sight of that. Kwashiorkor, or protein malnutrition, is a disease of poverty. Obviously, everything that can be done on the economic side has to be considered. Dr Clements spoke of the harassed mother, desperate, surrounded by her family. One reason why she is desperate all over the world is because she has to hunt for food for her family. There may be other priorities; there may be priorities before food. My opinion is that if we could satisfy the food requirements of that mother, we would go a long way towards solving some of the other social problems.

CLEMENTS: Dr Dean has posed three questions. The first is the best use of food resources—perhaps I should say natural resources; the second is the problem of the technical preparation of foods suitable for the weaning period of infants; the third is the ways in which the population can be persuaded to eat these foods. I think that we might spend a little time considering all of these, the first being the best use of food resources.

AYKROYD: I want to question Dr Dean's argument that the production of animal protein is necessarily more expensive, in terms of total agricultural resources, than the production of vegetable protein. Perhaps I could outline F.A.O.'s attitude on this point in a footnote to the Report, instead of going into it now.*

SCRIMSHAW: I would also like to add, in a footnote, specific evidence of the development of forages that do not compete with human food for increasing animal production.*

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* The following quotation from the Second World Food Survey (1952) throws light on the point under discussion—(W. R. Aykroyd):

'As pointed out in the first World Food Survey, when crops are fed to animals instead of directly to human beings they lose between 80 and 90% of their calorie value before they re-emerge in the form of meat and milk and eggs. This, of course, does not mean that for every calorie produced in the form of livestock products, four or five calories could have been obtained in other forms of human food. Much land used for grazing could not be put to any other effective use; much land at present used for grass or fodder crops could be made to produce food crops, but only of low yield and quality and at very high cost. Rotation of food crops with legume fodder crops is often essential for a sound system of soil conservation. To a very large extent animal and crop production are supplementary rather than competitive, and under the climatic and other conditions prevailing in many parts of the world a system of mixed farming gives best results for both. In some parts of the world animals constitute the main form of draft power in the absence of which crop production would seriously suffer. Nevertheless, there still remains a large field in which livestock can and do consume resources at the expense of human food. This applies especially to the excessive feeding of grain to livestock.'

AYKROYD: It is a large issue. Another point is that, while we are all in favour of the use of local foods, Dr Dean in his exposition was rather looking at the problem of protein malnutrition from the African tribal background, and did not take into account that there are large areas in the world, urbanized areas and even whole countries, in which there is plenty of protein malnutrition, and which are dependent to a large extent on imported foods. It doesn't necessarily follow that you must always look at the problem from the standpoint of local food supply. In fact, it has to be approached in the light of the situation prevailing in individual countries, which should be studied by nutrition workers and all the people concerned with food supply, and the appropriate solution found.

DEAN: I mentioned the danger of urbanization bringing kwashiorkor with it. But surely, whatever may be the case in particular instances, you would accept it as a general principle that food should be grown as near as possible to the place where it is to be used. It is only reasonable to try to cut out freight costs.

CLEMENTS: F.A.O. have shown that only 10% of the food produced in the world moves in international trade.

AYKROYD: By and large, it is home-produced food which is important. But there are exceptions. Some countries import something like 80% of their total food supply.

SANTOS: I agree with Dr Aykroyd. What is suitable for Africa is not necessarily suitable for Venezuela or Brazil.

HILL: There is one further point about resources that Professor Platt expounded at Istanbul, at the International Congress of Tropical Medicine (1953). That is the question of what happens to faeces in these countries. Normal faeces contain about 5% of the dietary protein, and also a certain amount of endogenous protein. In steatorrhoea you may get up to 40% of protein in the faeces. A day's output of faeces contains about 8 g. % of bacteria, which are pure protein. The problem arises, what is done with this? In primitive communities the people plough it back into the land and it produces cereals and vegetables. But with increased education, probably misapplied, or increased urbanization, we are turning that down the drain, and it never gets back to the land. What are we doing with this tremendous nitrogenous turnover that goes through the human being?

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* There are a number of reasons why one must not overlook the nutritional importance of doing everything possible to increase the production of animal products for the human diet. Dr Robert L. Squibb, on the basis of nearly 10 years of experience in animal husbandry in Central America has prepared the following comment:

'Regardless of the many theoretical calculations we can make regarding the inefficiency of converting foodstuffs to animal products as compared to production of plant foods of similar nutritional worth, we must consider the following: First, the use of all-vegetable protein mixtures requires considerable skill in compounding adequate diets. There is not enough margin of safety in such combinations, due to such a high variation among the nutrients of a single foodstuff. Second, data of the Instituto Agropecuario Nacional of Guatemala and the estimates of a number of tropical American soil scientists show that the best land use for over 80% of tropical American areas is increasing the return of land to pastures and forests. When one considers the conversion of the forages planted in these areas to highly palatable human foods, it is difficult to surpass the dairy cow. Third, even if the use of vegetable proteins did achieve a high state of efficiency there would still remain a considerable surplus of by-products derived from these same all-vegetable protein sources which only an animal can convert into palatable foods.'

DEAN: Nothing.

HILL: Exactly.

CLEMENTS: Dr Dean's second problem was the preparation of foods suitable for infants after weaning, and in particular, methods of substituting plant proteins for animal proteins. Has anyone any experience of this?

SCRIMSHAW: We have no experience with infants, but some trials that we have carried out on school children emphasize Dr Dean's point, and also raise an additional question.

The Institute of Nutrition of Central America and Panama was established in 1949; at the same time the countries concerned were persuaded to accept large quantities of skim milk for distribution in the schools. Although we had no data at that time, we were troubled because it was obvious that many of the countries would not have sufficient milk to continue such a programme when the supplies ceased; secondly, we were concerned about the possible effect of giving skim milk alone when other deficiencies might be present which milk would not prevent; finally, we had doubts of the capacity of some of the countries, from the standpoint of personnel, organization, transport, and so on, to handle such a programme. All three of these main doubts later proved to be justified, and in order to help the countries handle the problem when the skim milk was no longer available, we felt that the most important thing we could do was to try to find some means of carrying on the programme without milk. The obvious substitute seemed to be vegetable protein.

When we came to study the problem of vegetable protein versus animal protein, we found that there had been no studies which indicated clearly whether vegetable protein supplements or a diet containing only vegetable protein would be adequate even if the essential amino acids were supplied; in other words, whether there was an animal protein factor required over and above the essential amino acids. We therefore felt it necessary to compare the effects of a vegetable protein supplement with an animal protein supplement, and at the same time to evaluate the effectiveness of the type of supplementary school feeding which was being undertaken in Central America.

In anticipation of the possibility that an animal protein factor would be necessary, as suggested by experiments in animals which showed that vitamin B_{12} added to a vegetable protein diet increased growth, we arranged for groups of children in El Salvador and Guatemala to receive vitamin B_{12} in addition to the vegetable protein. Then our friends working on animal nutrition informed us that they were getting effects with animal protein factor concentrates which were different from those obtained with vitamin B_{12} alone, and that to cover this adequately, we should give some of our children this concentrate. Before the experiment was actually begun, it was announced that the active principal in animal protein concentrate was aureomycin, and the trial therefore included groups receiving aureomycin.

The first trial was done on groups of urban and rural school children in El Salvador. One group was given a complete animal protein lunch, with extra milk, egg, or meat, every day.

Table 18. *Adjusted gains in height and weight of school children in demonstration feeding programmes in El Salvador* (39)

School	Treatment	Starting date	No. children	Interval in months	Average monthly gain*	
					Height (cm.)	Weight (kg.)
		Urban				
Colombia	Animal protein lunch	ii. 1950	23	31	0·48	0·27
Roosevelt	Control	iii. 1950	30	30	0·49	0·26
		Rural				
Matazano	Control	vii. 1950	12	25	0·41	0·21
Comecayo	Animal protein lunch	v. 1950	22	28	0·40	0·20
Portezuelo	Veg. protein lunch	v. 1950	14	28	0·40	0·20
Portezuelo	Veg. protein lunch + B_{12}	v. 1950	17	28	0·48	0·20

Approx. L.S.D.$_{0\cdot05}$ for height = 0·11. Approx. L.S.D.$_{0\cdot05}$ for weight = 0·09.

* The data in this and subsequent tables are adjusted by multiple regression methods for differences in initial age, height and weight.

Another group was given a vegetable protein lunch, in which the base was soya, and then other vegetable proteins were introduced experimentally, such as peanuts and beans. The justification for using soya was twofold: first, it could be produced in the country if this proved practical, and secondly, we didn't know how to be sure of getting a reasonably adequate amino-acid combination in the diet, in advance of detailed chemical and biological studies of the whole proteins, without using the soya preparation. Finally, we gave vitamin B_{12} to part of the group receiving the vegetable protein lunch.

The results in summary were nil (Table 18). We did not succeed in demonstrating any advantage due to the lunch in either the urban or the rural group, compared with controls. In rural groups the growth rate was lower than in the urban children, but there was still no effect demonstrable from the lunch. We interpreted this to mean that we had not been able to improve the diet sufficiently, because the children were definitely retarded in growth. In El Salvador 50% of the diet is eaten at the noon meal, and it is very difficult to *substitute* for 50% of the diet and obtain substantial improvement. We concluded from that that a lunch programme in a country in which the noon meal provides the principal dietary component is the wrong way to go about it; a mid-morning snack would have been preferable. We would enter a plea that such habits be taken into consideration.

It should be added that the vitamin A intake of these children, even with the lunch, was not satisfactory, and may have been limiting the growth response. In other schools in El Salvador and Honduras the administration of dried skim milk alone was associated with a mild increase in the incidence of follicular hyperkeratosis, and a failure of the vitamin A level in the blood to rise seasonally, as would have been expected.

In another experiment in Guatemala a snack was given as a mid-morning meal, as early as possible, so as not to interfere with lunch. An animal protein snack, given over nearly 2½ years, did appear to have some effect (Table 19). The height increment increased from 0·33 to 0·38 cm. per month. A vegetable protein snack with or without added vitamin B_{12} or aureomycin had approximately the same effect. Here then, is an improvement with supplementary feeding, but it failed to reach statistical significance. (The change should be 0·14 per month to be significant at the 5% level.)

In this experiment there was no detectable difference between the animal and vegetable protein snacks, and added B_{12} or aureomycin had no effect. It was originally postulated that adding animal protein factor or vitamin B_{12} to a diet could have no effect as long as amino acids and other vitamins were limiting, and the only fair way to test the action of animal protein factor was to give it in addition to a vegetable protein supplement. But in one village we tried giving two groups of about twenty children 50 mg. of aureomycin, or 20 mg. of vitamin B_{12} daily for 15 months without any other supplement (Table 18).

Unfortunately, the controls were in two other villages, and this weakens the conclusion. The controls grew at the rate of 0·33 cm. per month. During the 15-month period in which B_{12} or aureomycin were given, the rate of change in height adjusted for differences in age and weight was 0·44 and 0·48 cm. per month. These differences are significant. In the 12 months following the suspension of these two substances, the rate in the group previously receiving aureomycin dropped to a little less than the control rate; this drop was significant. In the group that received B_{12} the drop was slow and not significant.

In a subsequent experiment we tested penicillin, penicillin plus B_{12}, and a placebo, in a larger group. No beneficial effects from the penicillin were observed (40).

Table 19. *Adjusted gains in height and weight of school children in demonstration feeding programmes in Guatemala*

School	Treatment	Starting date	No. children	Interval in months	Average monthly gain	
					Height (cm.)	Weight (kg.)
San Antonio	Control	vi. 1950	43	11·4	0·33	0·17
Santa María	Animal protein snack	v. 1950	81	23·5	0·38	0·21
Magdalena	Veg. protein snack	iii. 1950	83	28·2	0·39	0·18
Magdalena	Veg. protein snack + B_{12}	iii. 1950	28	25·3	0·43	0·24
Magdalena	Veg. protein snack + aureomycin	iii. 1950	29	21·7	0·42	0·27

Approx. L.S.D.$_{0\cdot05}$ for height = 0·14. Aprox. L.S.D.$_{0\cdot05}$ for weight = 0·10.

In a still larger and more critically designed trial 200 children in two towns were given aureomycin, penicillin and placebos. The preliminary figures indicated that aureomycin produced a significant response in height increment in both towns. In one town, but not in the other, penicillin also had a significant effect. This raises the question of the extent to which we can think of the problem of vegetable protein supplementation in terms only of amino acids, or whether we will have to take into consideration an additional factor such as vitamin B_{12} or other still unknown substances with 'animal protein factor' activity.

I do not consider that any of the experiments done anywhere in the world including our own, give a conclusive answer. This is something that must be critically investigated in the future.

MACKAY: Why is it that in the second experiment, in which a snack was given, you got an increase in the growth rate, whereas in the first experiment you didn't?

SCRIMSHAW: There are two different situations. The reason, I think, is that in the first experiment in El Salvador, dietary surveys show that the lunch we gave improved the intake of animal protein—from 15 to 32 g. a day in the urban group and from 8 to 23 g. a day in the rural group; but it made very little difference to the intake of calories or of total protein. In Guatemala, on the other hand, where a supplement was given, although the home diet was uncontrolled, surveys showed that we did produce a substantial increase in calories and total protein, as well as in animal protein and other factors. In Guatemala also the children are more retarded, and in some respects the diet is poorer. Therefore you would expect differences to show up better.

GOPALAN: We have carried out some growth studies with vitamin B_{12} in children in an orphanage, from 4 to 10 years old, whose diets were deficient in animal protein. We studied them for about 6 months, and then we put one group on B_{12} and the other on a placebo, and studied them for another 6 months. I can confirm Dr Scrimshaw's observation that vitamin B_{12} did not appreciably influence the growth rate.

MACKAY: We have been studying the influence of these factors on about 800 children; we first of all surveyed the growth rate and the general dietary background, for between 1 and 2 years. The 800 children were divided into four groups, one being given a placebo, another B_{12}, another aureomycin, and the last aureomycin plus B_{12}. We have completed the work, but can't report on it, because we are in the process of calculating the results.

DEAN: I have done a small experiment of this kind in a school that I have more or less under my control. The diet there consists of plantains, when obtainable, with maize, groundnuts, and meat once or twice a week; no other animal protein is eaten during the week. One group of children was given about 50 μg. of B_{12} per day; another group was given a multivitamin preparation providing about 7 μg. of B_{12} a day; and a third group received a placebo. Like Dr Scrimshaw, we were unable to demonstrate any effect from the addition of B_{12} or the other vitamins.

I think that if there is already enough vitamin B_{12} in a diet, it is illogical to expect any effect from adding more; also, the amount of B_{12} that will show a beneficial effect may be related to the amount of total protein in the diet, because we know that the requirements for B_{12} alter with the amount of protein.

I want to make an apology to Dr Gyorgy, who asked me to state specifically where my interests in this matter really come in. My real interest is in the prevention of kwashiorkor, and in the utilization of plant proteins. The work that we have done on kwashiorkor has been done because it offers a wonderful chance for testing the value of plant protein mixtures. If we can cure a child with kwashiorkor by giving a plant protein mixture, we should be able eventually to suggest some ways in which prevention will be possible. We have also a chance of seeing the effect of substances such as vitamin B_{12}, when added to a plant protein mixture. As I have already said, my experiments of that kind have hardly begun.

Scrimshaw: We all hope it will turn out that the human can synthesize sufficient B_{12}, presumably in his gut, but if he does not, then we need to know the minimal amount of animal protein needed in the diet. The experiments that I quoted suggest that 13 g. of animal protein is enough. It may turn out that only 5 g. are needed, or it may turn out that no animal protein is needed. This is a critical point that must be determined in the planning of the best utilization of the food supply of a country. We are not suggesting that supplementation by B_{12} should be considered, but that the minimal requirement of animal protein should be determined. Similarly, the purpose in studying aureomycin is not, under any circumstances, to urge the use of aureomycin but for the light it may shed on the operation of an animal protein factor.

Clements: Would anyone like to take up the question of education? When you have decided on the best preventive measures, how do you put them over to the individual mother?

Williams: I am glad you have come back to that. We have been studying how to bring the horse to the water, but we haven't yet talked much about making him drink. That, I think, is a big problem, how to get nutrition into the backyard, where it really matters.

Waterlow: Professor Platt made an observation which is relevant to this question, and also to the point Dr Clements made earlier about the drain on the mother. He measured the time that women in a Nyasaland village spent pounding grain. This amounted to about 4½ hours a day. This meant that with all her other tasks the mother had no time or energy left to absorb education, improve her cooking, grow vegetables, etc. Therefore, for education to be worth while, some of this load must be taken off her shoulders, e.g. by the introduction of a village mill.

Williams: In an experiment we did in Benghazi we had a central hospital with fifty children, who always had their mothers with them. The nurses, from the day they came into the hospital, were not only working with the children in hospital but also in the area round about. The town had a population of about 30,000, and we had fourteen different welfare centres in it. The nurses would go out one day a week to the welfare centre and to the homes, and the mothers of that area would bring children to be seen by the nurse. In that way, from the very start, the nurses learned the whole set-up; they knew the family, they met the father, they met the other children. If a child was sick and had to go into hospital, the nurse actually knew what sort of conditions it was going back to.

The actual food that was going into the children was observed. The mother always came into hospital with her child and helped in the care of the child, so that when she went home she knew exactly what to do and how to prepare the foods that were being used. We used various methods of adapting the local diet without any additions of imported food. For instance, the mother was shown how to cook the food properly. It might be a case of beating an egg in with the maize meal, if she could afford it—and she nearly always could—or buying milk to mix up with banana. In some cases, where the food was coarse, she was instructed to get an old tin and punch holes in the bottom with a nail and rub the food through that.

SCRIMSHAW: Isn't that what we generally speak of as a community approach, and isn't everybody agreed that in rural prevention work there must be a community approach?

WILLIAMS: I think it is an individual approach, too, because in some communities there seems to be no association at all between the hospital and the extension work that is going on. In the Gambia report, for instance, it said that mothers were getting instruction about food through infant welfare centres, but that is rather like Marie Antoinette saying, 'Why don't they eat cake?' because in some places there aren't any welfare centres and in other places they are perfectly useless. What is a welfare centre? What is it supposed to do? How are the people trained?

CLEMENTS: I don't think we can lay down here any hard-and-fast rules to apply the world over, nor can we take an example from any one country and apply it to another country. You must use whatever machinery exists in a country—the village leader, the nurse, the public health nurse, or whoever is there. It is the job of the local authorities to use them, but one of the difficulties is to get the local authority interested, and to set up the machinery.

SCRIMSHAW: Wouldn't it be worth while to re-emphasize that prophylaxis must involve not only the pre-school children and the school children but also the pregnant woman, and the woman during lactation? The fact is that many of these children are born of malnourished women, and so begin life with lessened reserves. In Guatemala, for example, in over 100 newborn babies we have found vitamin A levels in the blood of 12 μg. %, or less, which is about one-third the level in many other parts of the world (Fig. 21).

CLEMENTS: Do you have other figures showing that the newborn starts with a definite handicap?

SCRIMSHAW: Yes; the vitamin A happens to be the most dramatic.

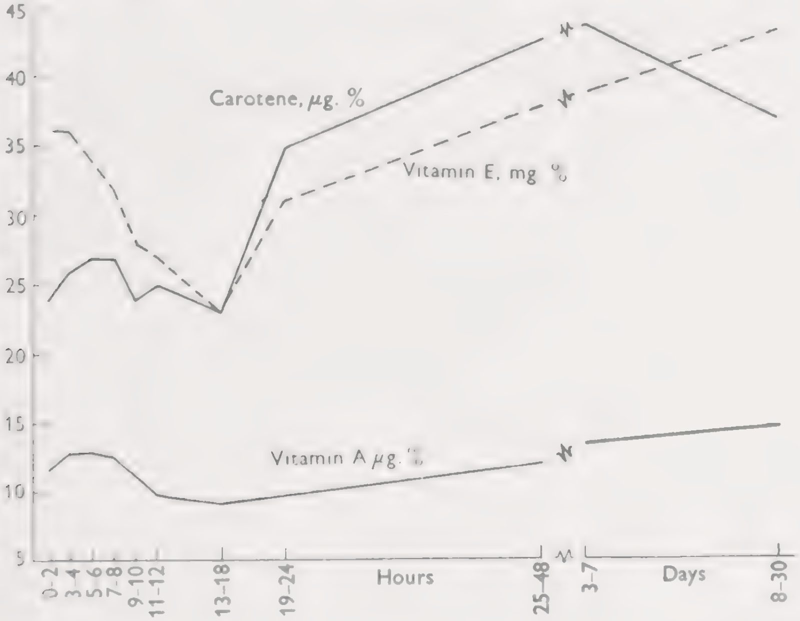
GOPALAN: On the question of nutrition education—

CLEMENTS: Should we say 'education for living'?

GOPALAN: Yes. I just want to re-emphasize the fact that, in addition to primary dietary deficiency, one factor which I feel is important in precipitating florid signs of protein malnutrition is alimentary infection. Education must therefore be directed towards the avoidance of unhygienic feeding habits, which are very prevalent in some of these rural communities. I know that by doing that we are not going to reduce protein malnutrition as such, but we can reduce much of the morbidity and the mortality which arise from it.

SCRIMSHAW: That is also a general principle applicable in many parts of the world.

SANTOS: I think that one of the easiest ways to educate people in malnourished areas is, as has been done in Brazil, to choose well-settled areas where the problems can be worked on, and then allow representatives of other communities to come in and see the results.



Text-fig. 21. Vitamin levels in Guatemalan infants in the first month after birth.

AYKROYD: Mr Chairman, may I say that this question of education for living, to use your expression, which includes education in nutrition, is one to which great attention is now being given by the international bodies generally—by the United Nations, by F.A.O., and by W.H.O.—and the whole question of extension work, as it is called, is being very intensively studied in its various aspects. A good deal of assistance is being given to countries, at their request, in developing extension services of various types—public health extension services, agricultural extension, home economics services, and so on. There seems to be, throughout the world, a general move in that direction as one of the methods of improving the condition of rural peoples, and I think it is particularly our job as nutrition workers to ensure that in rural community education, nutrition, of which the problem we are now considering is a part, be given adequate place. That was the point emphasized by the Gambia conference, and by a number of other regional nutrition conferences.

Burgess: May I add one point? Bringing in a number of skills to this field is something that has interested the World Health Organization. In the prevention of malnutrition, as in the prevention of other diseases, it is necessary to know people's attitude towards the particular problem that is facing them. With even the limited amount of work that has been done in W.H.O., we have found that the cultural anthropologist is often of great help.

Clements: The time has now come to close this conference. I know that we have not been able to cover completely any of the subjects we have discussed. Nevertheless, I think the conference has been successful. We have had the benefit of several disciplines—the scientist, the clinician, and the administrator, to name only three. We have had the benefit of experience from many different parts of the world. Lastly, for our present purpose I think it has been an advantage that we had no formal agenda, and that under the stimulus of Dr Fremont-Smith we adopted what may be called the Macy or 'free-for-all' technique of discussion.

What has been our purpose? Not to solve problems, because they are not solved round a table; nor simply to exchange information, nor to make formal recommendations. I think our main purpose has been to clarify our minds. The theme of this conference has been 'where do we go from here?' Before we can go anywhere we must define our starting-point; we must see clearly what we know and what we don't know, what are the gaps in our knowledge, and what the points of conflict. This is a prerequisite for progress. The next few years will show whether I am right in thinking that we have achieved this, at least in part.

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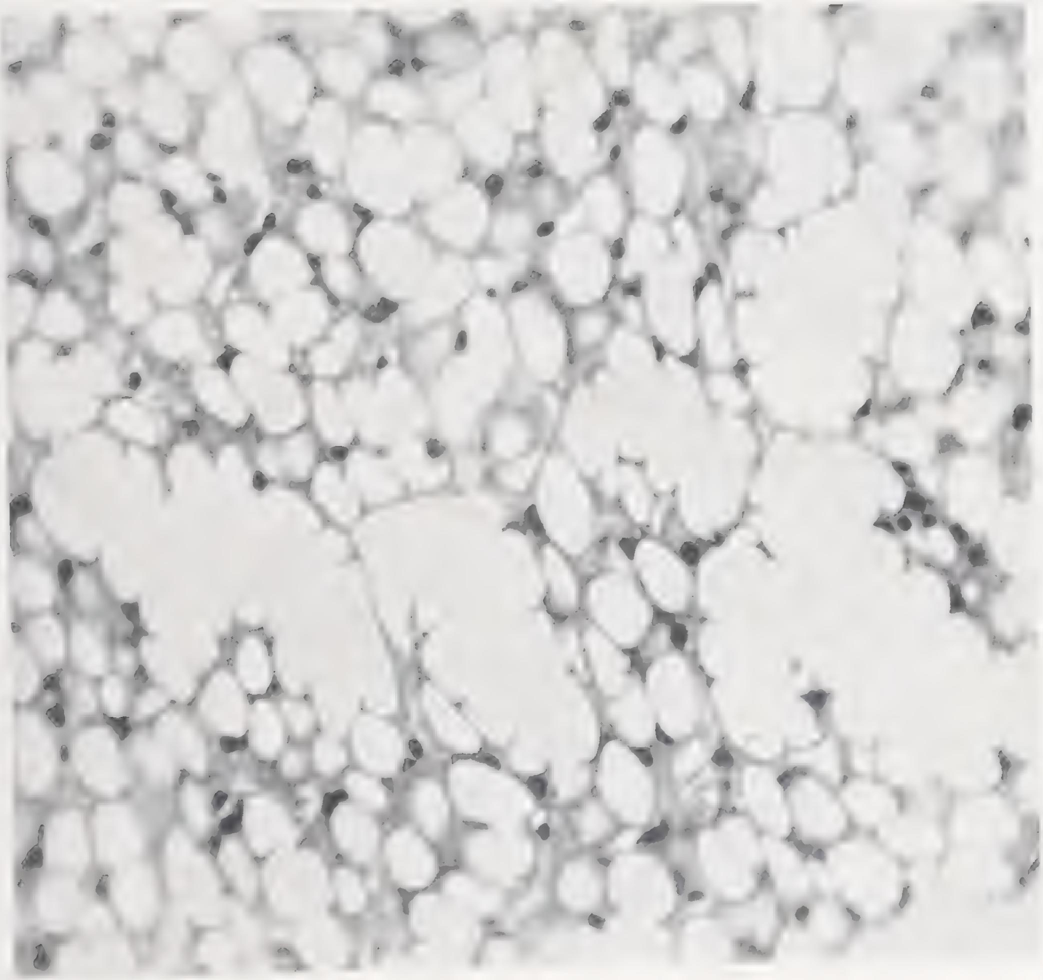
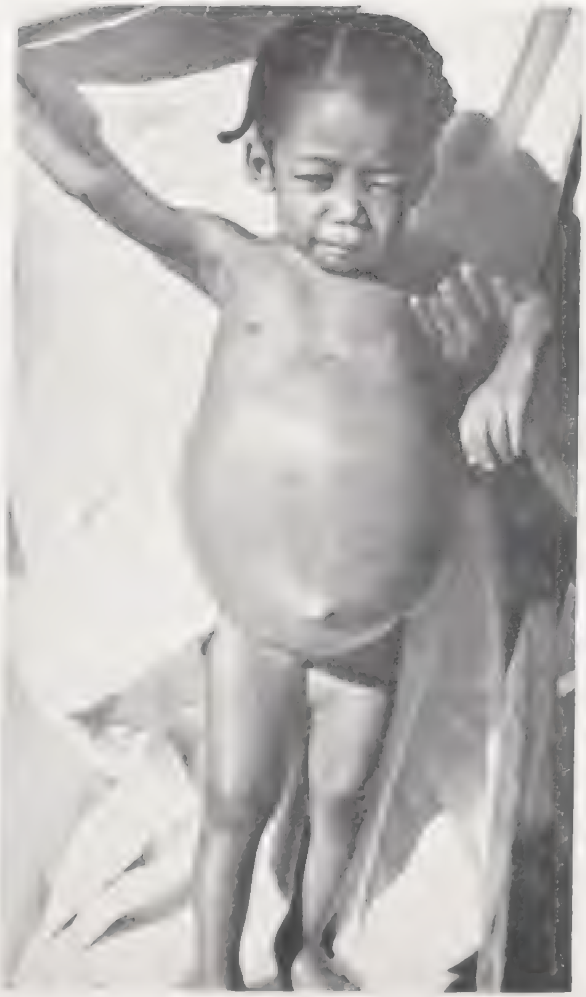
PLATES

PLATE I



Section of fatty liver from a case of kwashiorkor.
Paraffin section. Haematoxylin and eosin.

PLATE 2



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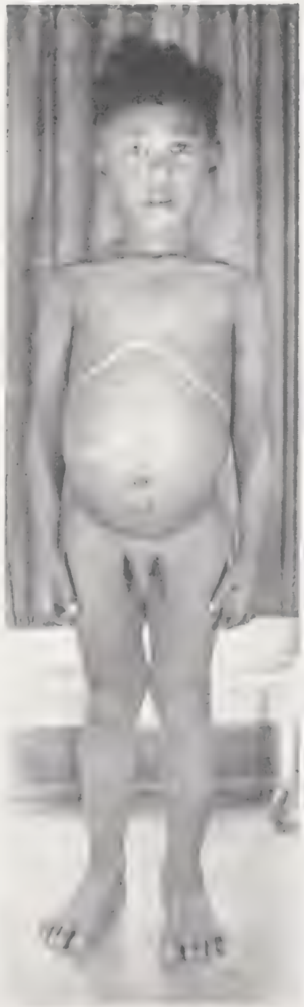

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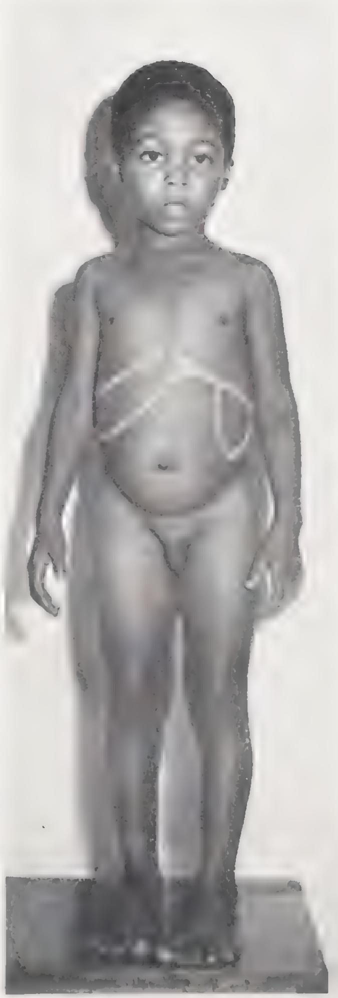

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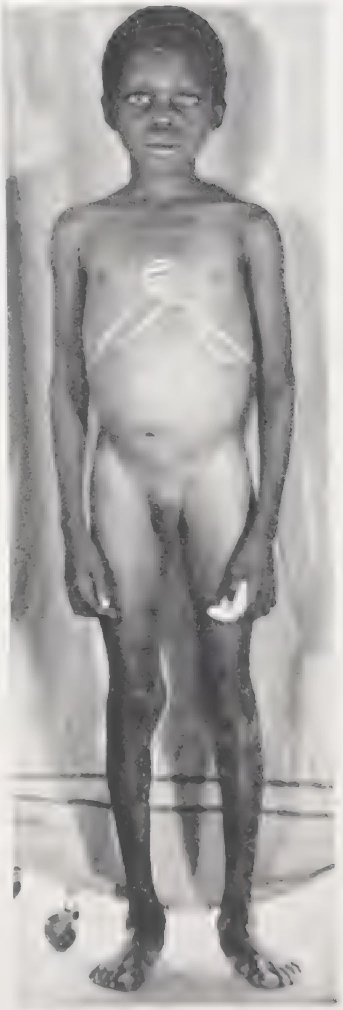
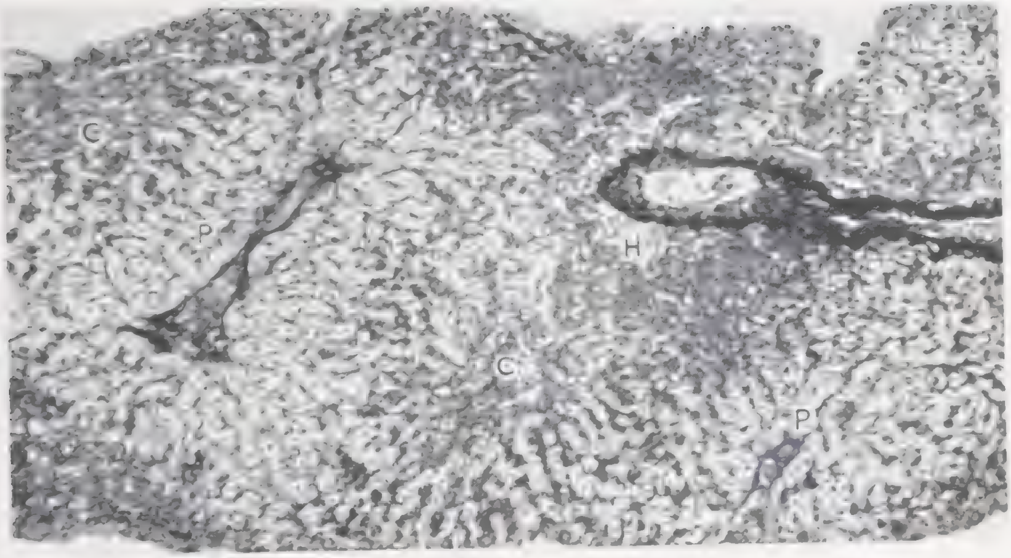


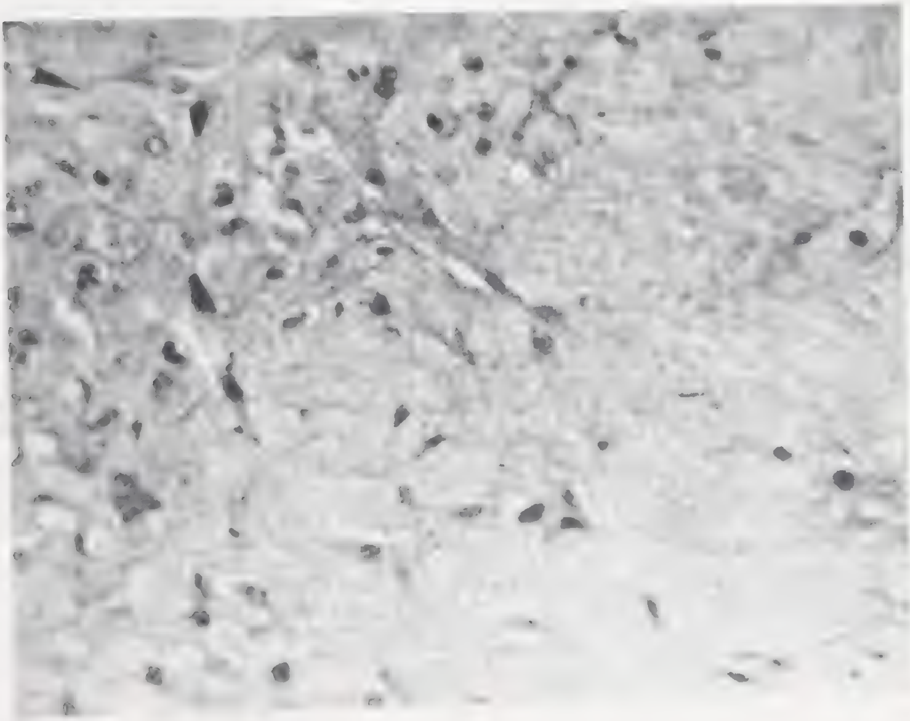
4

PLATE 3



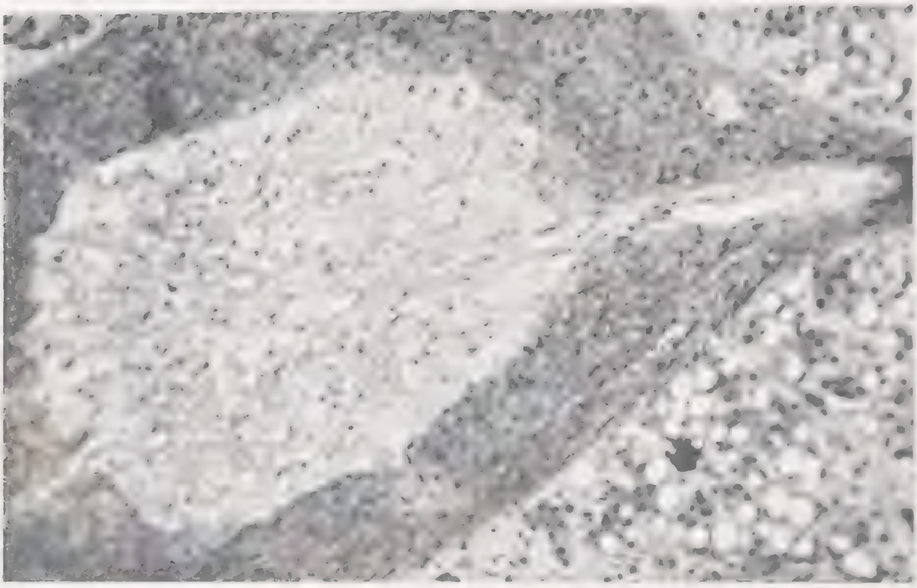
1

Lab. no. 53/283. Needle biopsy. Girl aged 5 years; acute abdominal distension for 1 week, hepatomegaly + + +. There is congestion in centrolobular areas (*C*) leaving portal areas (*P*) unaffected. At *H* sublobular vein with thickened intima. Mallory trichrome stain, × 60.



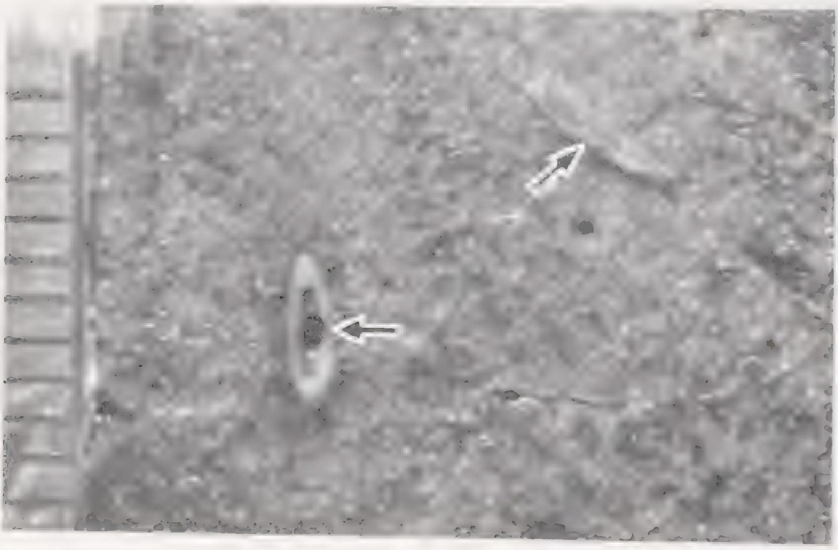
2

Lab. no. 53/539. Needle biopsy. Girl aged 6 years. Very marked centrolobular compression and disappearance of liver cell cords, i.e. [illegible]lal congestion with formation of 'blood lagoons'. In left upper part of picture non-compressed liver cell cords of a portal area are shown. Haemat.-azophlox. stain, × 400.



1

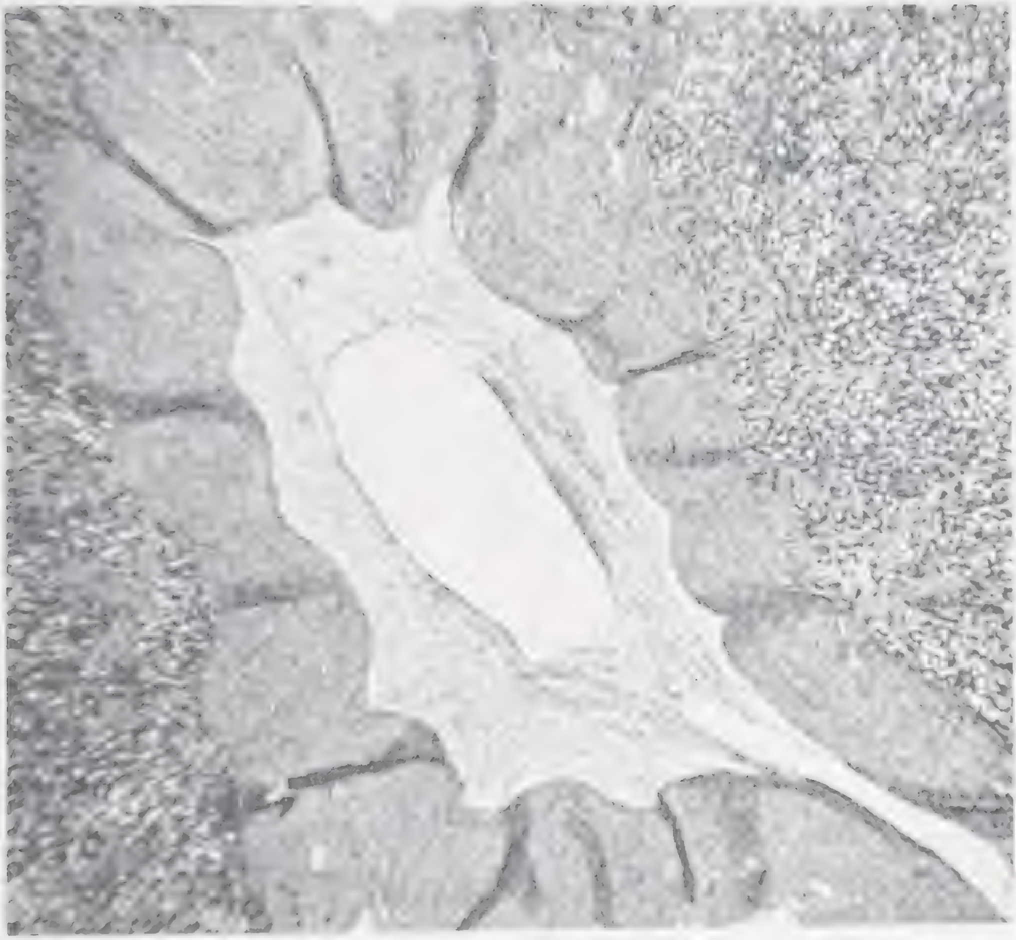
Lab. no. PM 138. Boy aged 10 months; at autopsy there were jaundice, ascites and hepatomegaly. Organization of intimal swelling. Orcein-fast green F.C.F. stain, × 140.



2

Same case as (1) above. Cut section of liver. Arrows point at vessels which show a gelatinous intimal thickening, having completely (upper) and partially (lower) occluded the lumen. Scale in mm.

PLATE 5



Histological section of vessel shown in Pl. 4(2). Same case, haemat.-azophlox. stain, × 70.

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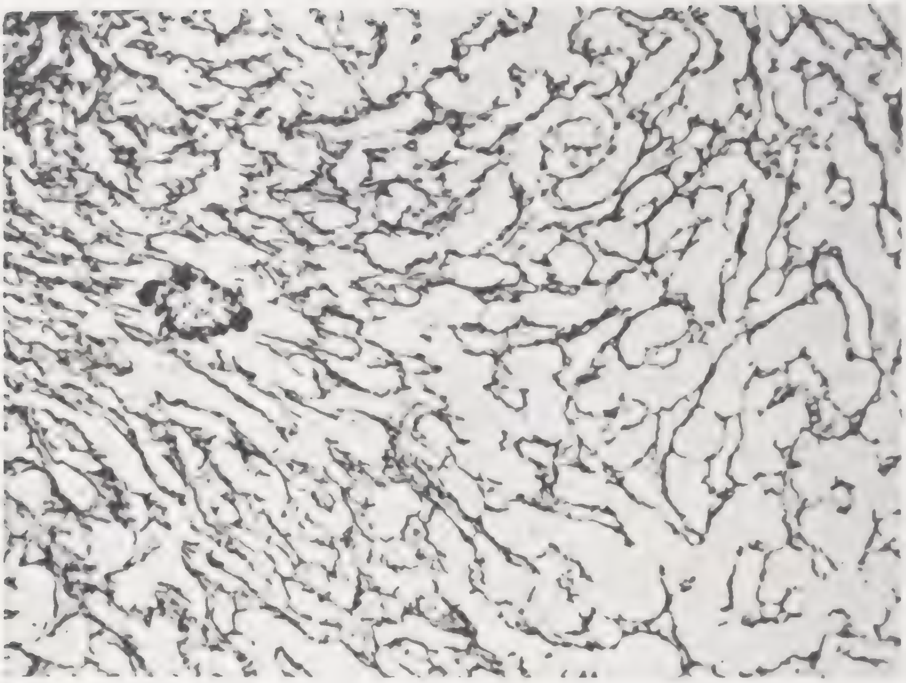
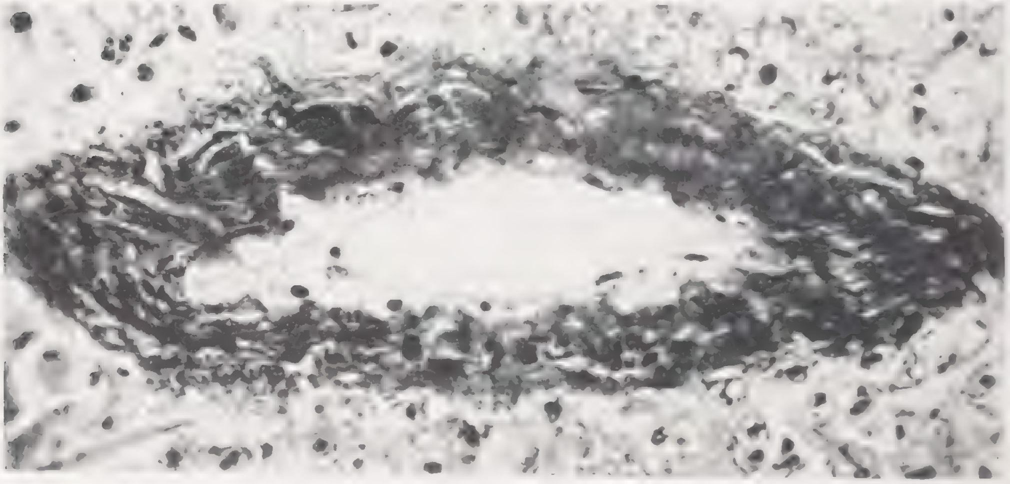


1

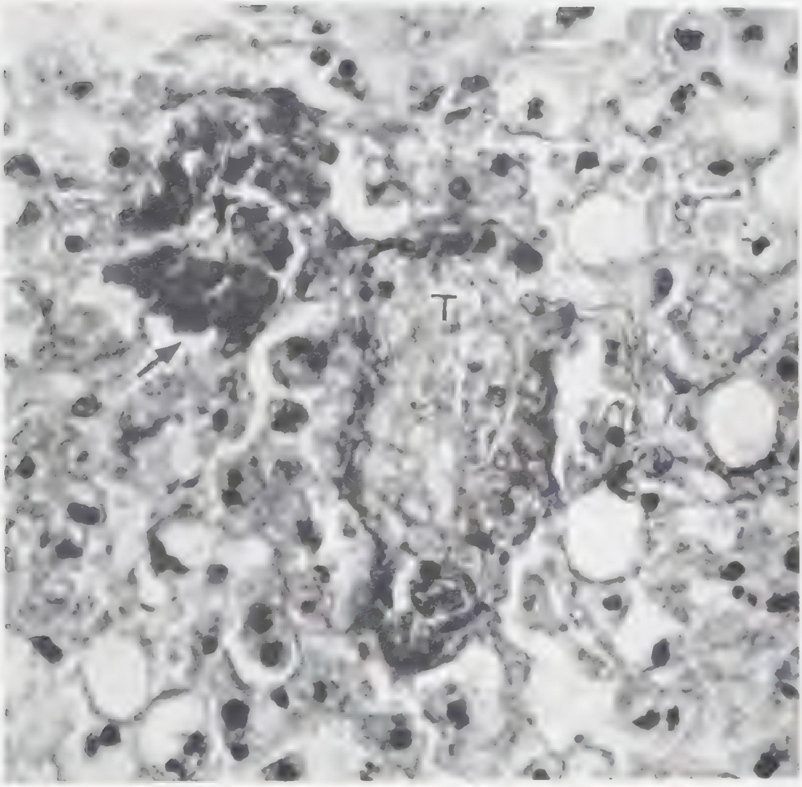
Lab. no. 53 380. Needle biopsy. Girl aged 11 months. At left a partly occluded centrolobular vessel. Condensation and proliferation of reticulin fibres in the centrolobular area. The portal zone (right half of picture) is unaffected. Reticulin stain, × 300.



2

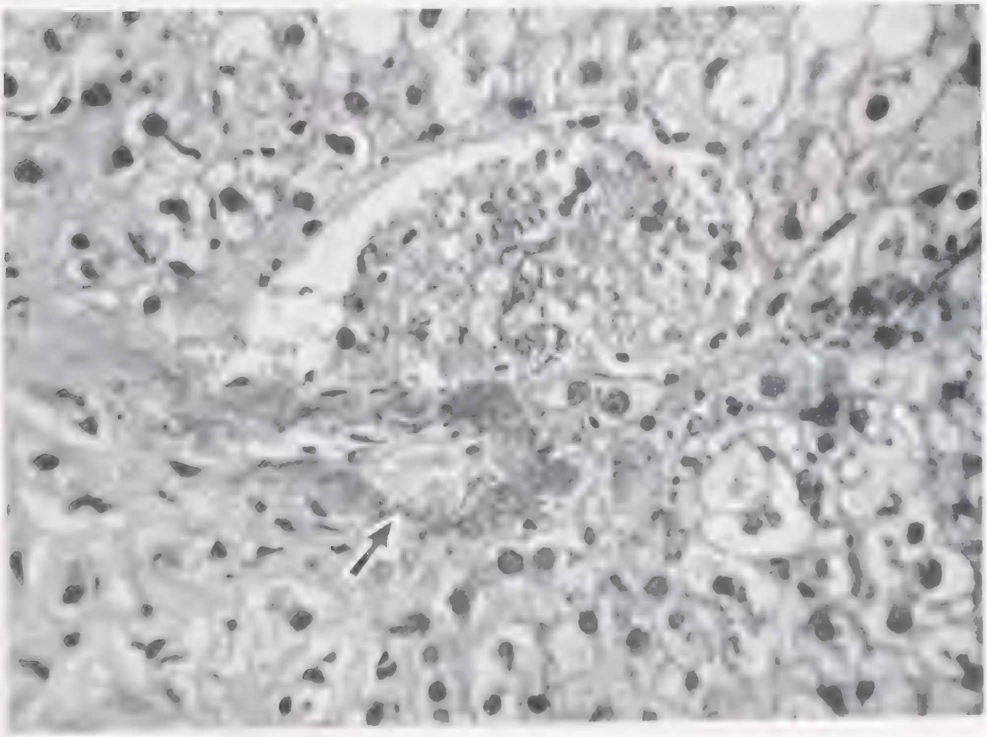
Lab. no. PM 96. Girl aged 14 months at autops[illegible] ascites and hepa[illegible] Sublobular vein with slight intimal swelling of th[illegible] wall otherwise thickened. Orcein-fast green F.C.F. stain, × 450

PLATE 7



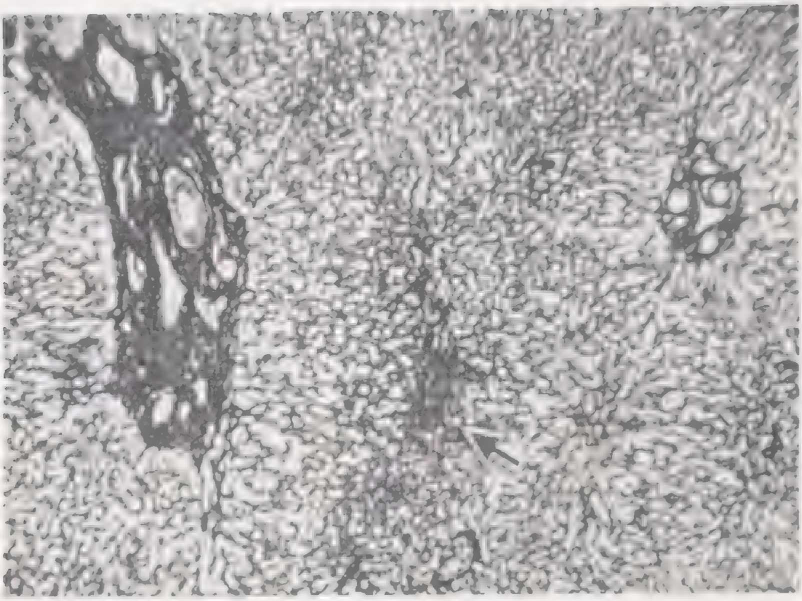
1

Same case as Pl. 6(2). (?) Contracted sublobular vessel at arrow with distended tributary (*T*). Mallory trichrome stain, × 400.



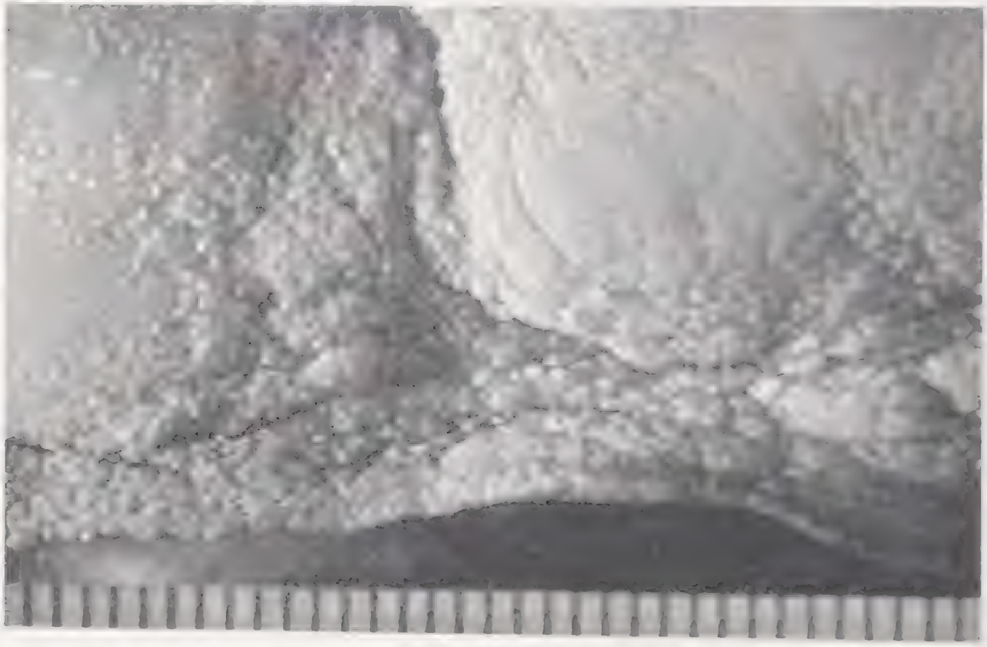
2

Lab. no. 53 439. Needle biopsy. Same case as Pl. 6(1), 3 weeks later. Occluded vessel at arrow; above it a newly formed collateral blood channel. Orcein-fast green F.C.F. stain, × 400.



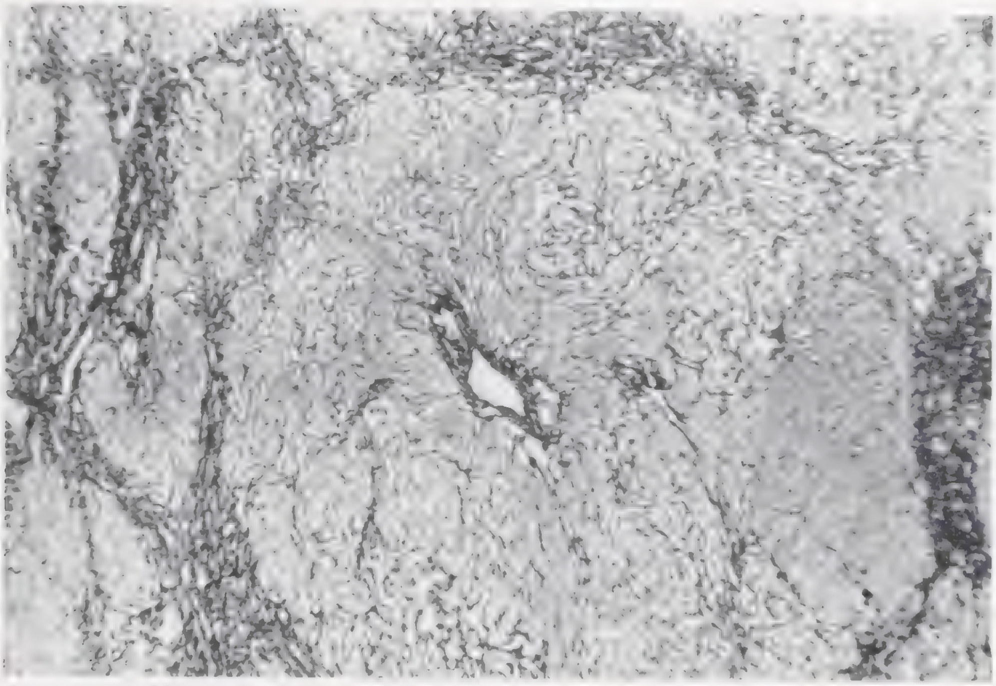
1

PM96. Same case as Pl. 6(2). Non-portal fibrosis around occluded centrolobular vessel at arrow. Portal triads unaffected. Reticulin stain, × 50.



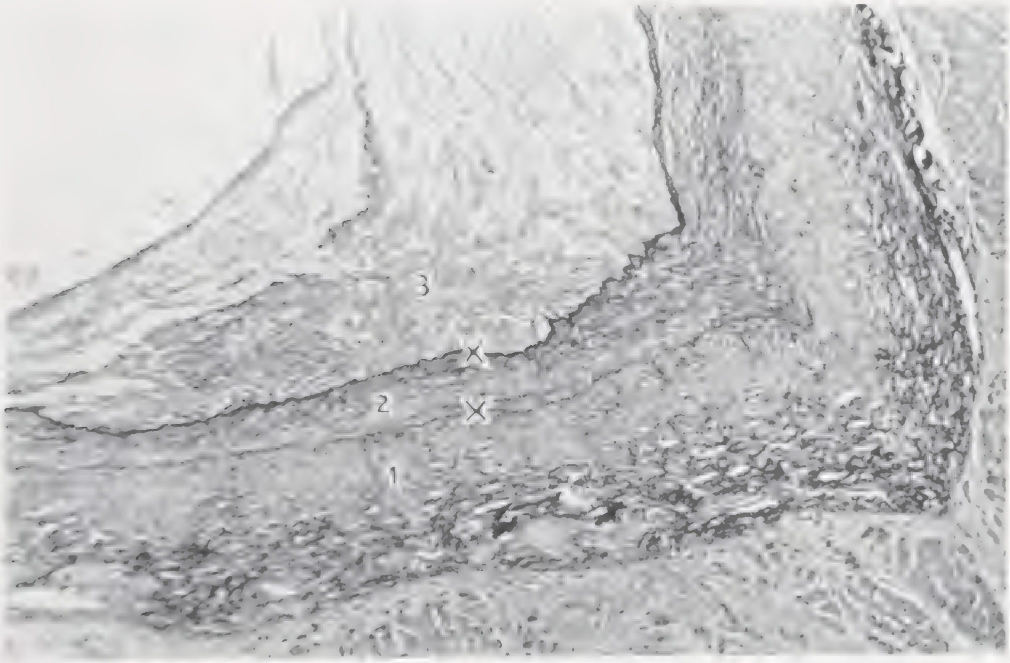
2

Lab. no. PM60. Boy aged 9 years; at autopsy there was a diffuse finely granular cirrhosis, ascites and ruptured oesophageal varices. Anterior surface of liver, scale in mm.



1

Same case as Pl. 8(2). Non-portal cirrhosis leaving the portal area (centre) relatively unaffected. Reticulin stain, × 90.



2

Same case as Pl. 8(2). Original media at 1, organized intimal swelling of previous attack at 2, recent acute intimal swelling at 3. Both the original internal elastic membrane and that subsequently formed (after first attack) are shown at *X*, *X*. Elastica-van Gieson, × 75.

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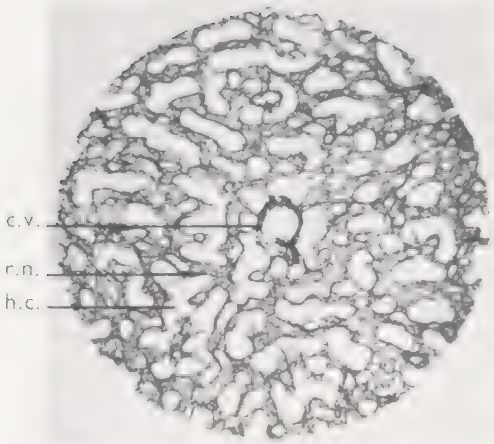
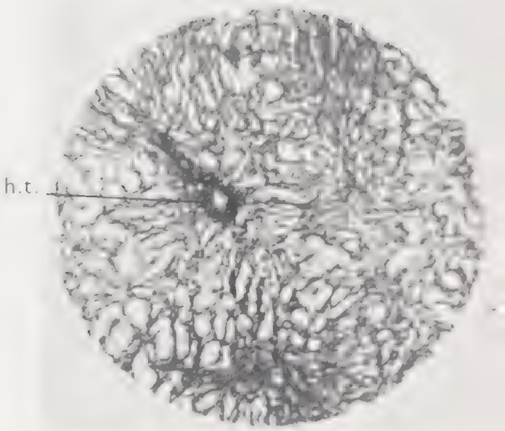


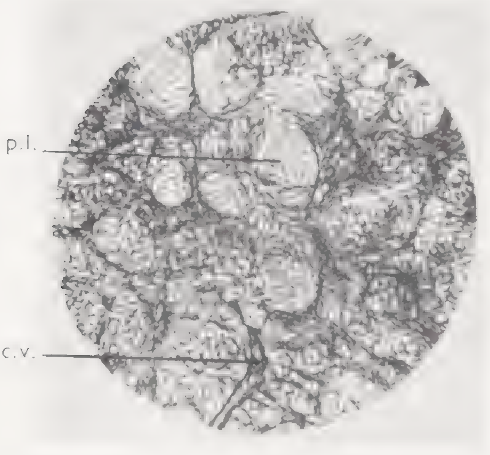
1

Reticulum of normal liver. Note the central vein (*c.v.*) and the reticulum network (*r.n.*) of the sinusoidal capillary bed. The hepatic cords (*h.c.*) are unstained and are represented by the empty spaces in the figure. Foot and Menard's silver carbonate impregnation technique.



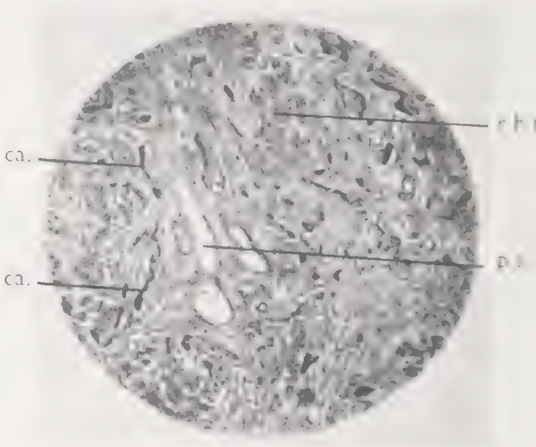
2

'Infantile biliary cirrhosis.' Hepatic terminal (*h.t.*) showing sclerosis of walls and narrowing of lumen; the reticulum of the sinusoidal capillary bed is disorganized. Foot and Menard's silver carbonate impregnation technique.



3

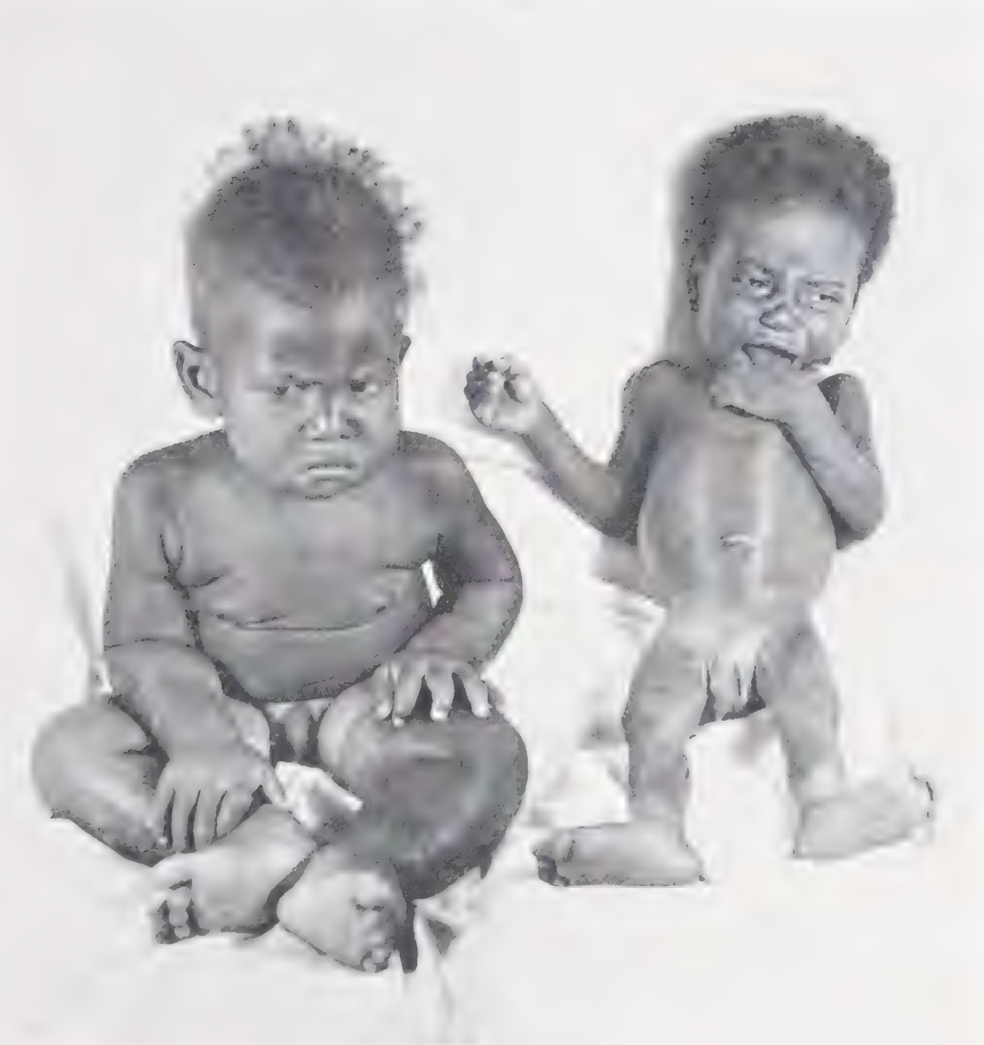
'Infantile biliary cirrhosis.' Reticulum of the liver showing regeneration of the parenchyma (unstained) with the formation of pseudo-lobules (*p.l.*). Note the absence of central veins in the pseudo-lobules; *c.v.*, collecting vein showing partial obliteration of its lumen. Foot and Menard's silver carbonate impregnation technique.



4

'Infantile biliary cirrhosis.' Liver showing the prominent and deeply staining pseudo-bile canaliculi (*ca.*) in the connective tissue network; most of them enclose only a potential lumen; *r.h.n.*, regenerated hepatic nodule; *p.s.*, portal space. Ehrlich's acid haematoxylin and eosin.

(From Radhakrishna Rao, M.V. (1935). *Indian J. med. Res.* **23**, 69. Reproduced by courtesy of the editor *Indian Journal of Medical Research*.)



1 Typical 'sugar-baby' type of Jamaican kwashiorkor.

2 Marasmic kwashiorkor.

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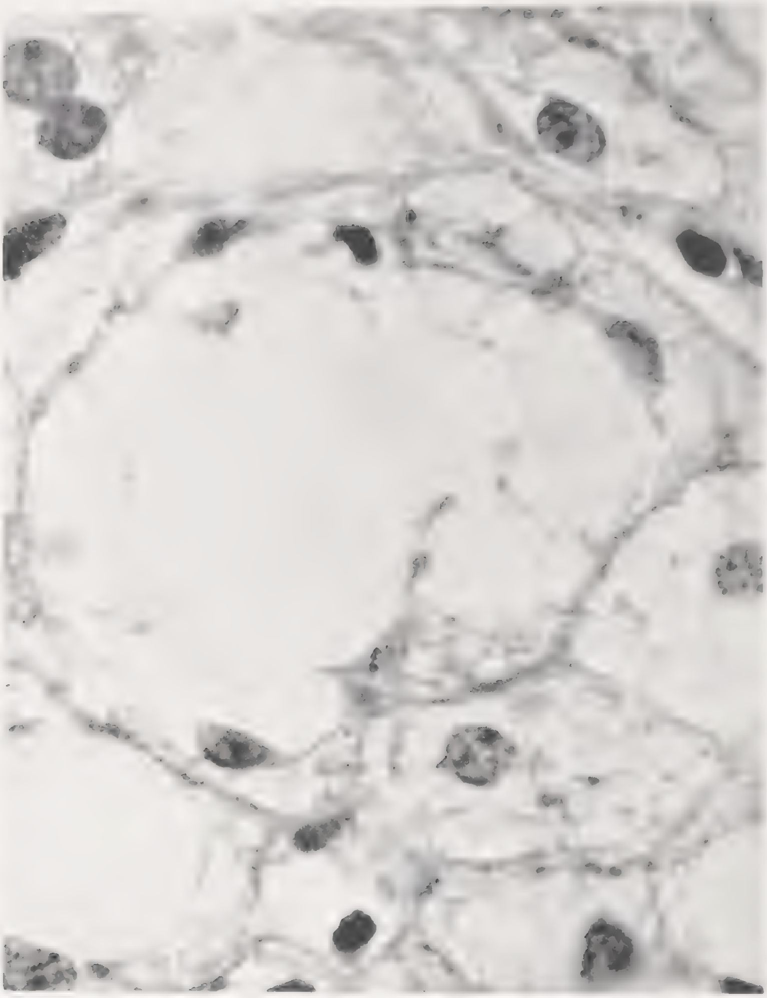
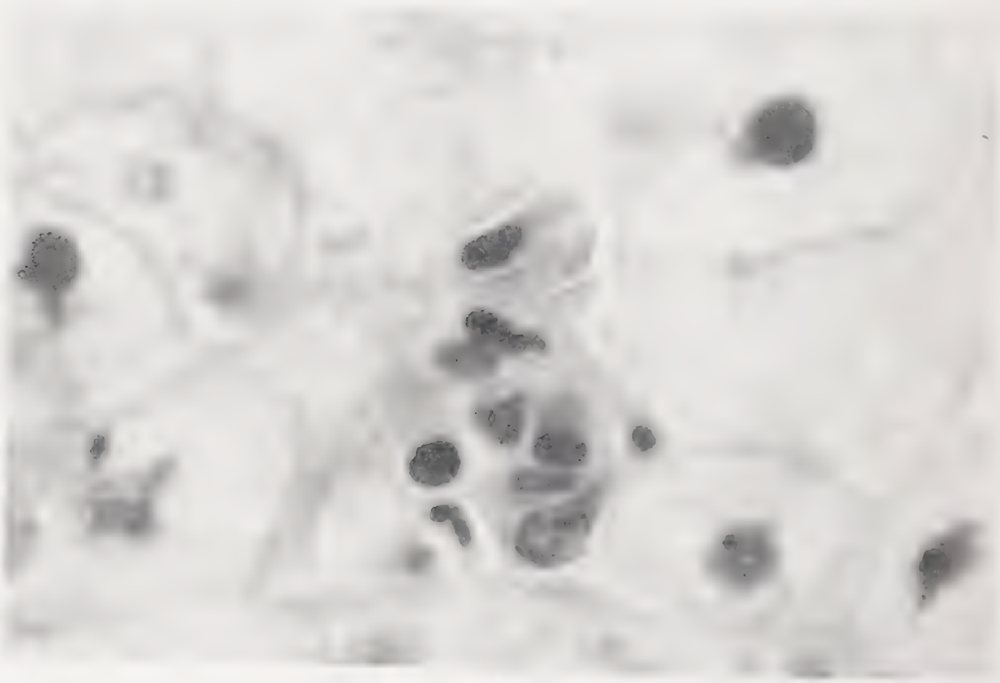


1

Lab. no. 53 276. Needle biopsy. Girl aged 8 years, hepatomegaly, firm liver. Histologically grade II fatty change with periportal fibrosis. The picture shows a fatty cyst. Haemat.-azophlox. stain, × 1620.

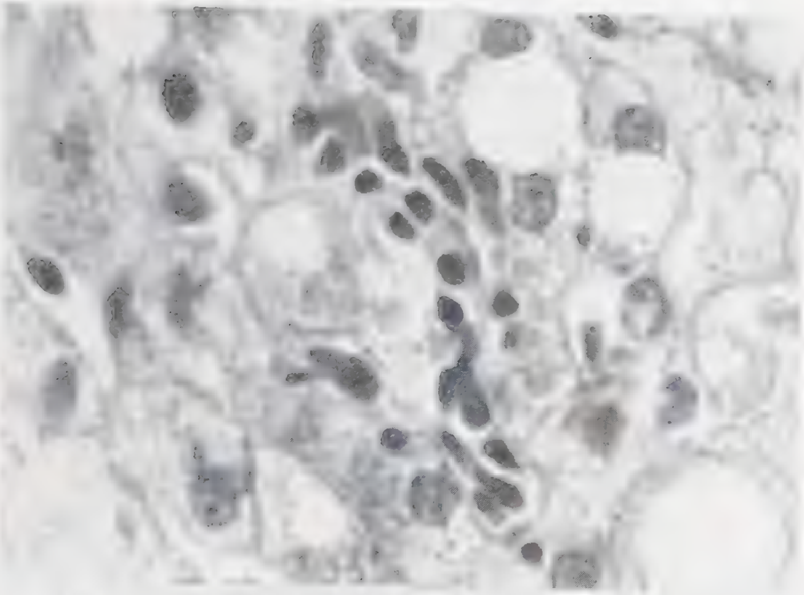


2

Lab. no. 52 253. Girl aged 4 years with marasmus. Needle biopsy 3 weeks after hospitalization shows accumulation of cells (histiocytes and lymphocytes) in the sinusoids. Haemat.-azophlox. stain, × 1620.

PLATE 13

1



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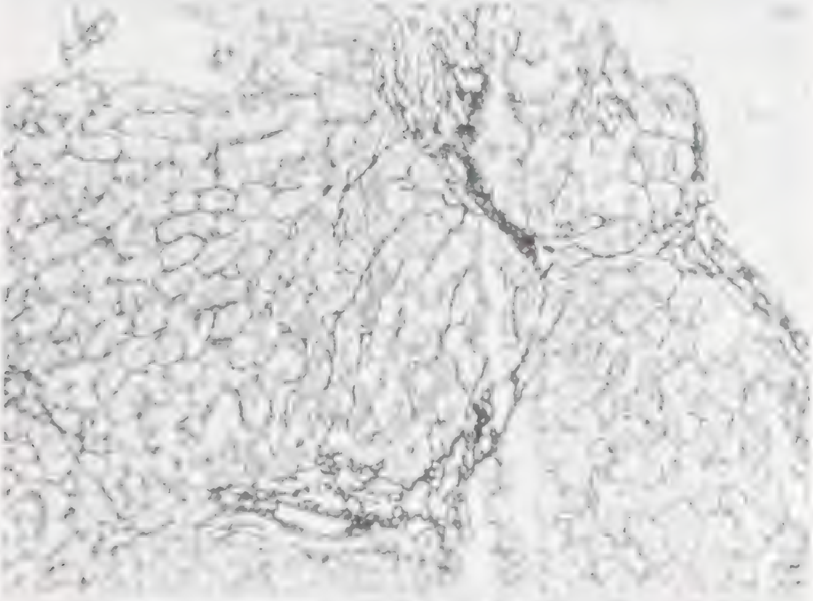
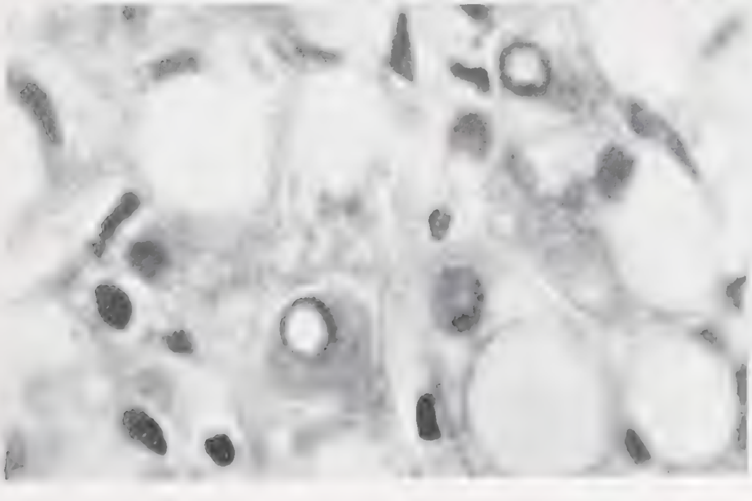
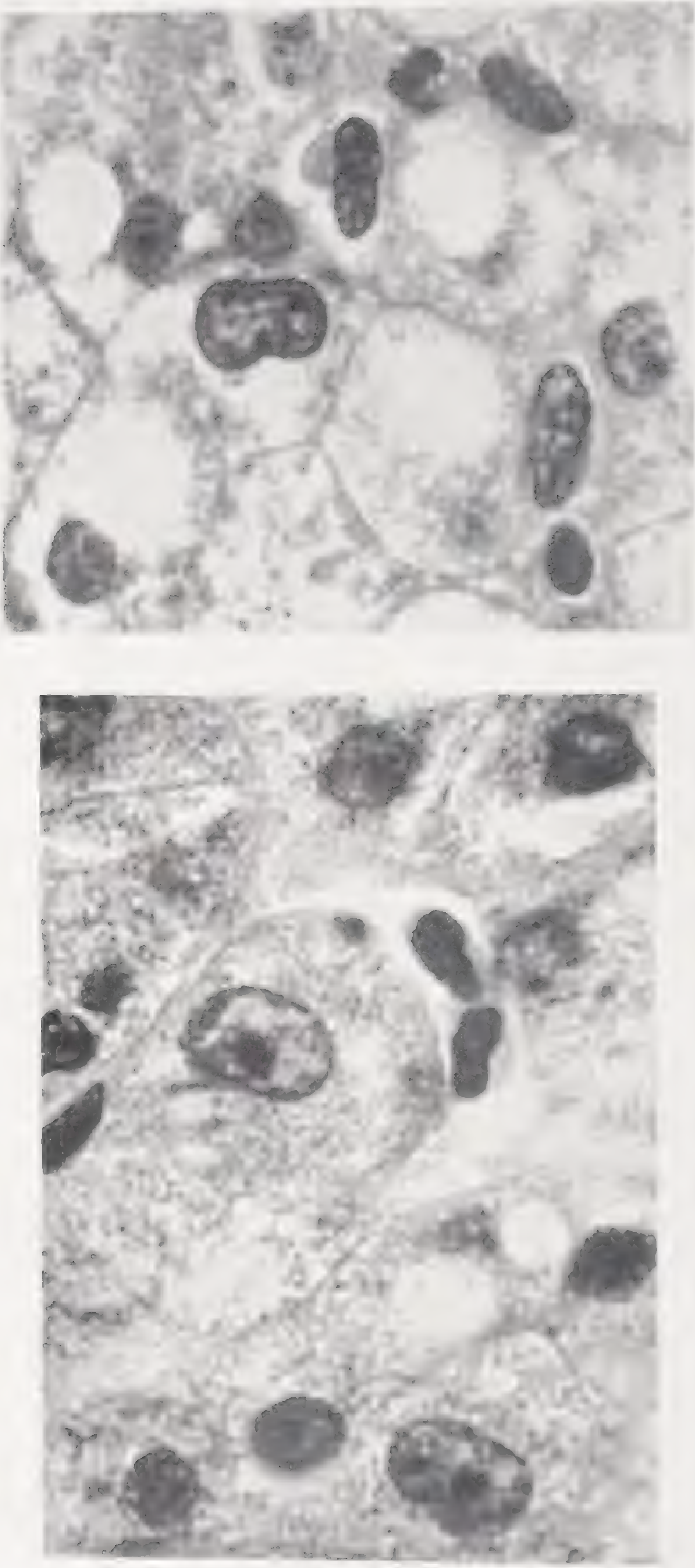


3



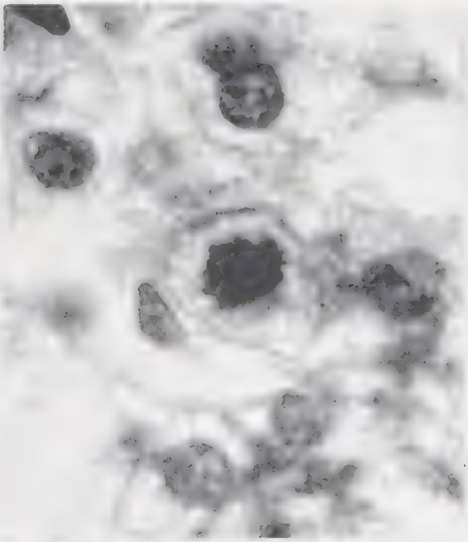
1. Lab no 52 206. Boy aged 14 months with marasmic kwashiorkor. Needle biopsy. The picture shows histiocytic and lymphocytic cells in the sinusoids. The liver had a grade II fatty change. Haemat.-azophlox. stain, × 1620.
2. Lab no 52 293. Girl aged 2½ years, with marasmic kwashiorkor. Needle biopsy showing periportal fibrosis. Reticulin stain, × 180.
3. Lab no 52 200. Boy aged 13 months with kwashiorkor. Needle biopsy showing nuclei with glycogen vacuoles. Haemat.-azophlox. stain, × 1620.

PLATE 14



Amitosis. Needle biopsies from patients with kwashiorkor aged respectively 2 years and 15 months. Haemat.-azophlox. stains, × 1620

1



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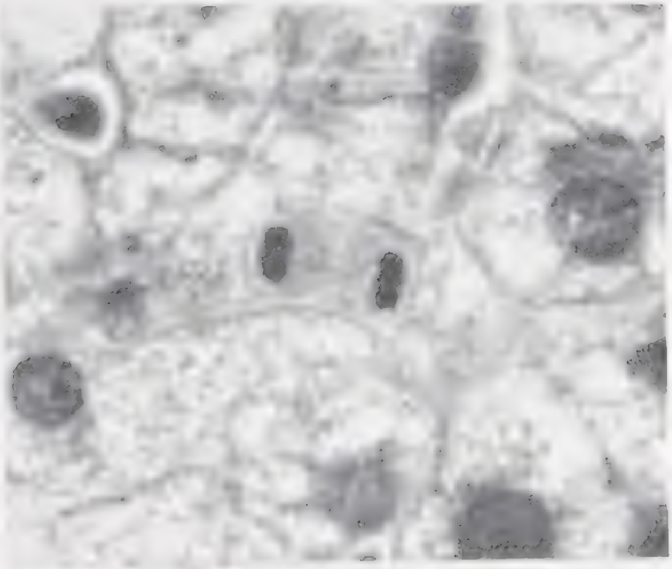

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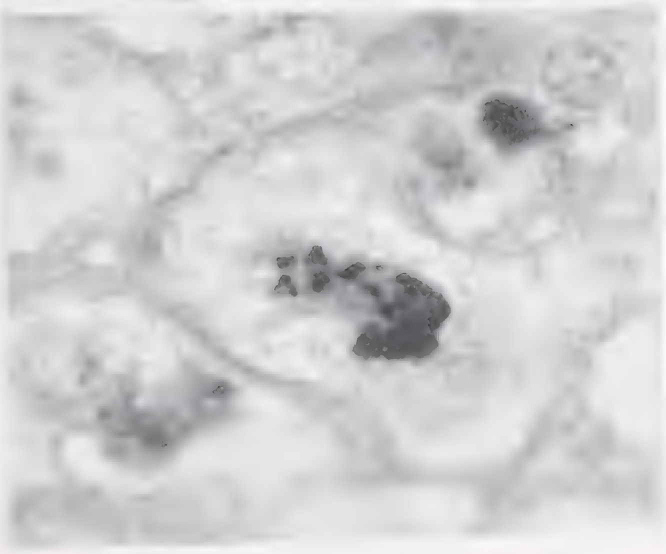
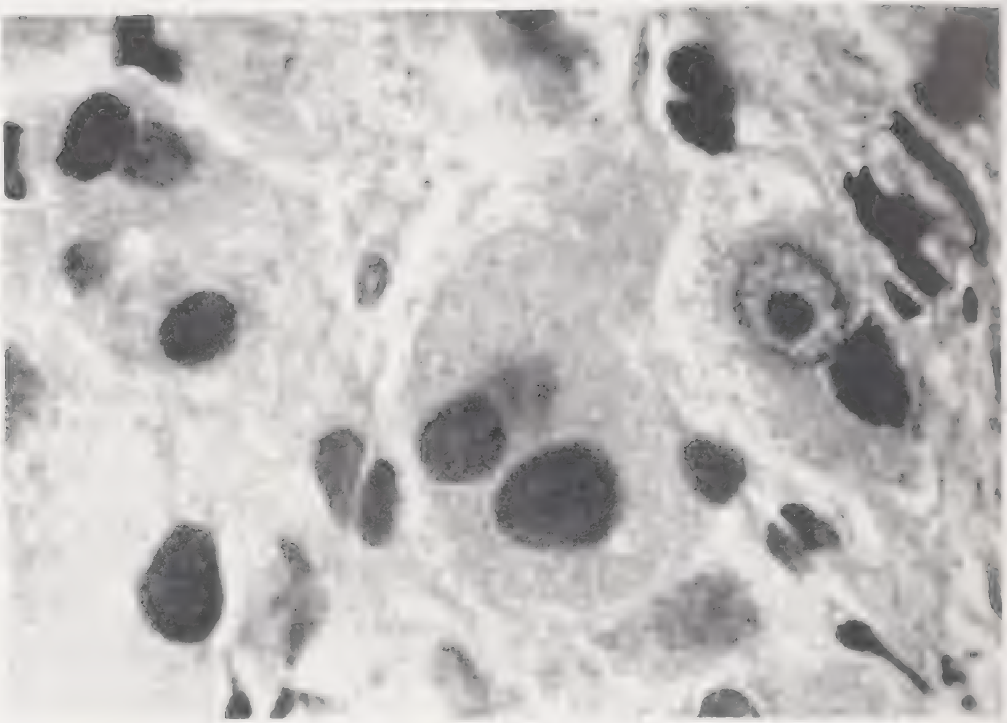


1, 2. Same patient as Pl. 13(1). Mitoses in parenchymal cells prophase and telophase. Haemat.-azophlox. stains, × 1620.

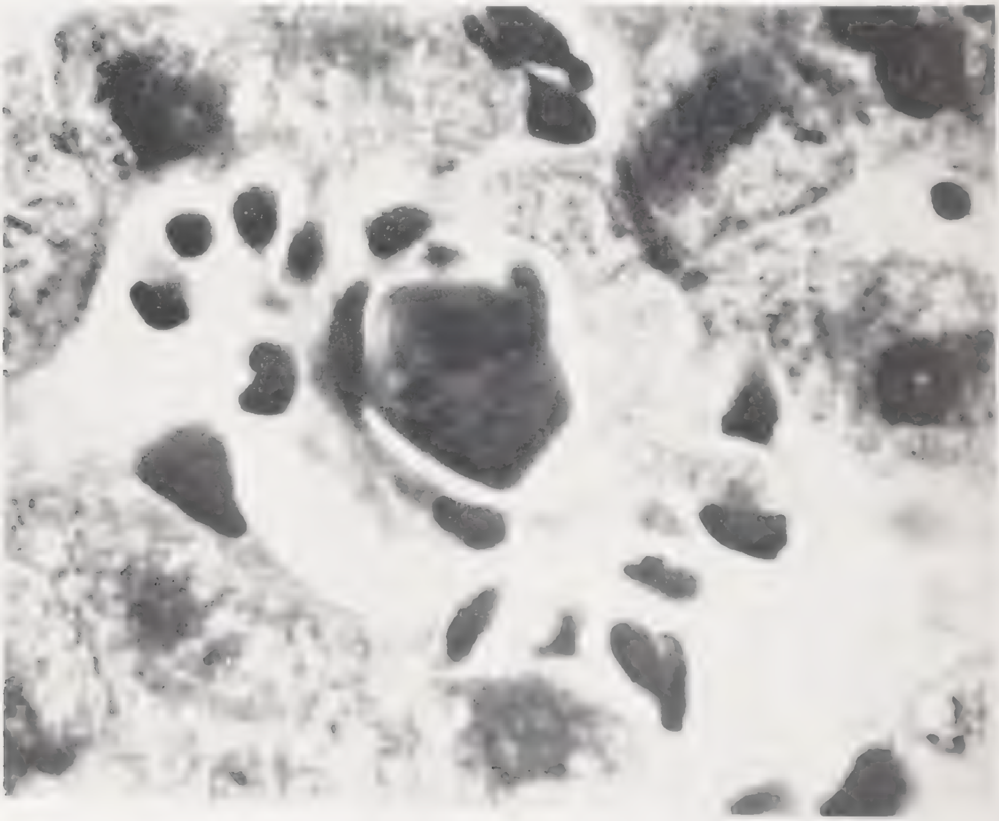
3. Lab. no. 52 107. Boy aged 8 years in 'normal' nutritional state, admitted for ankylostomiasis and a mild broncho-pneumonia. Picture shows a so-called 'exploded' mitosis. Haemat.-azophlox. stain, × 1620.

PLATE 16



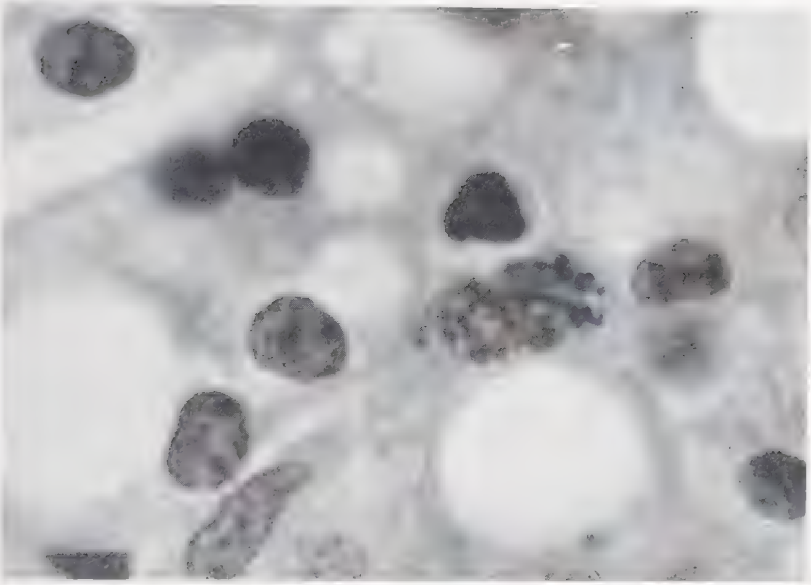
1

Lab. no. 52 286. Boy aged 9 years with cirrhosis of the liver. Needle biopsy showing double-nucleated parenchymal cell with one nucleus undergoing pyknosis. Haemat.-azophlox. stain, ×1750.



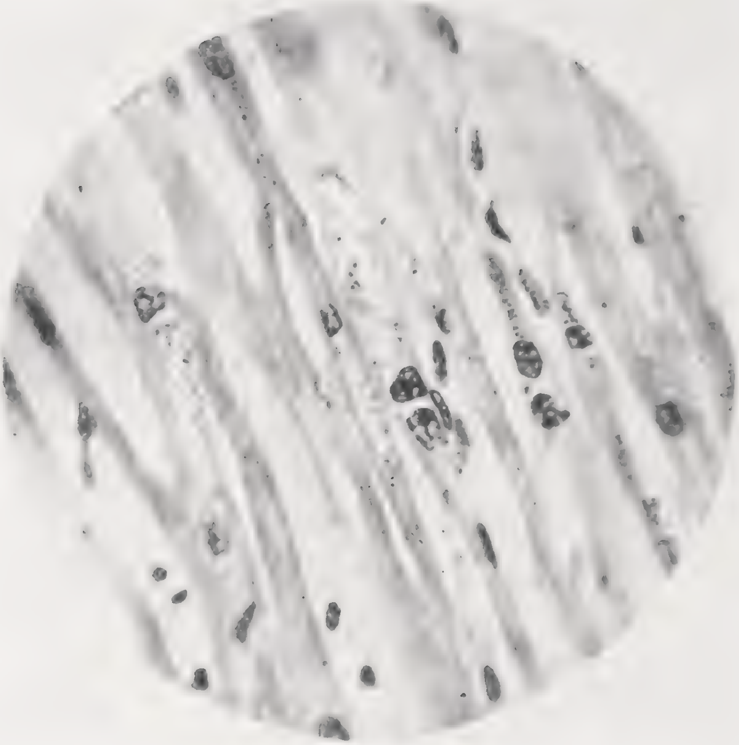
2

Lab. no. [illegible] Eosinophilic degeneration of parenchymal cell. [illegible] surrounding the degenerated cell. Haemat.-[illegible]



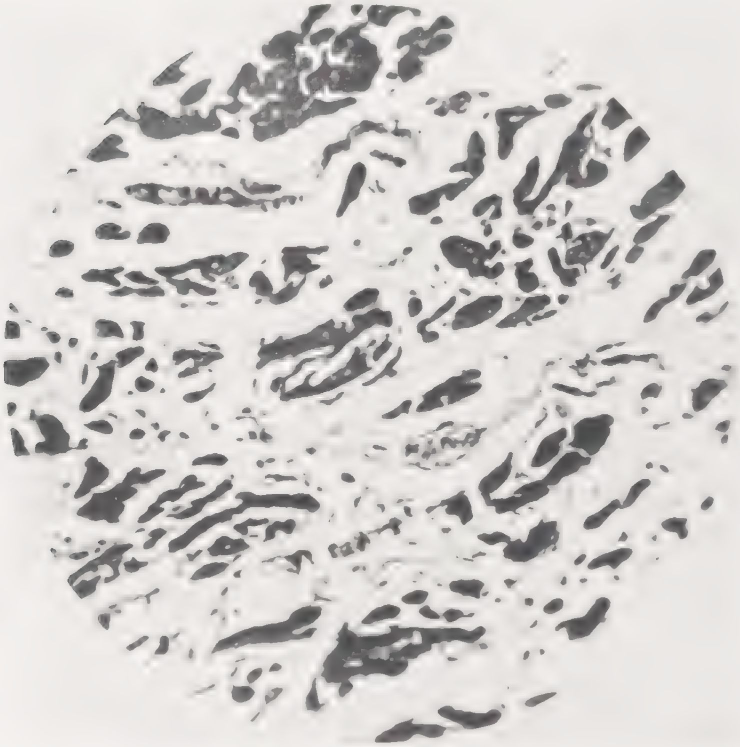
Lab. no. 53 538. Girl aged 17 months with kwashiorkor; needle biopsy showed dark brown pigment in Kupffer cells (see picture), but also in the portal triads. Haemat.-azophlox. stain, × 1500.

PLATE 18



1

Section of heart from a case of adult nutritional oedema, showing brown atrophy.

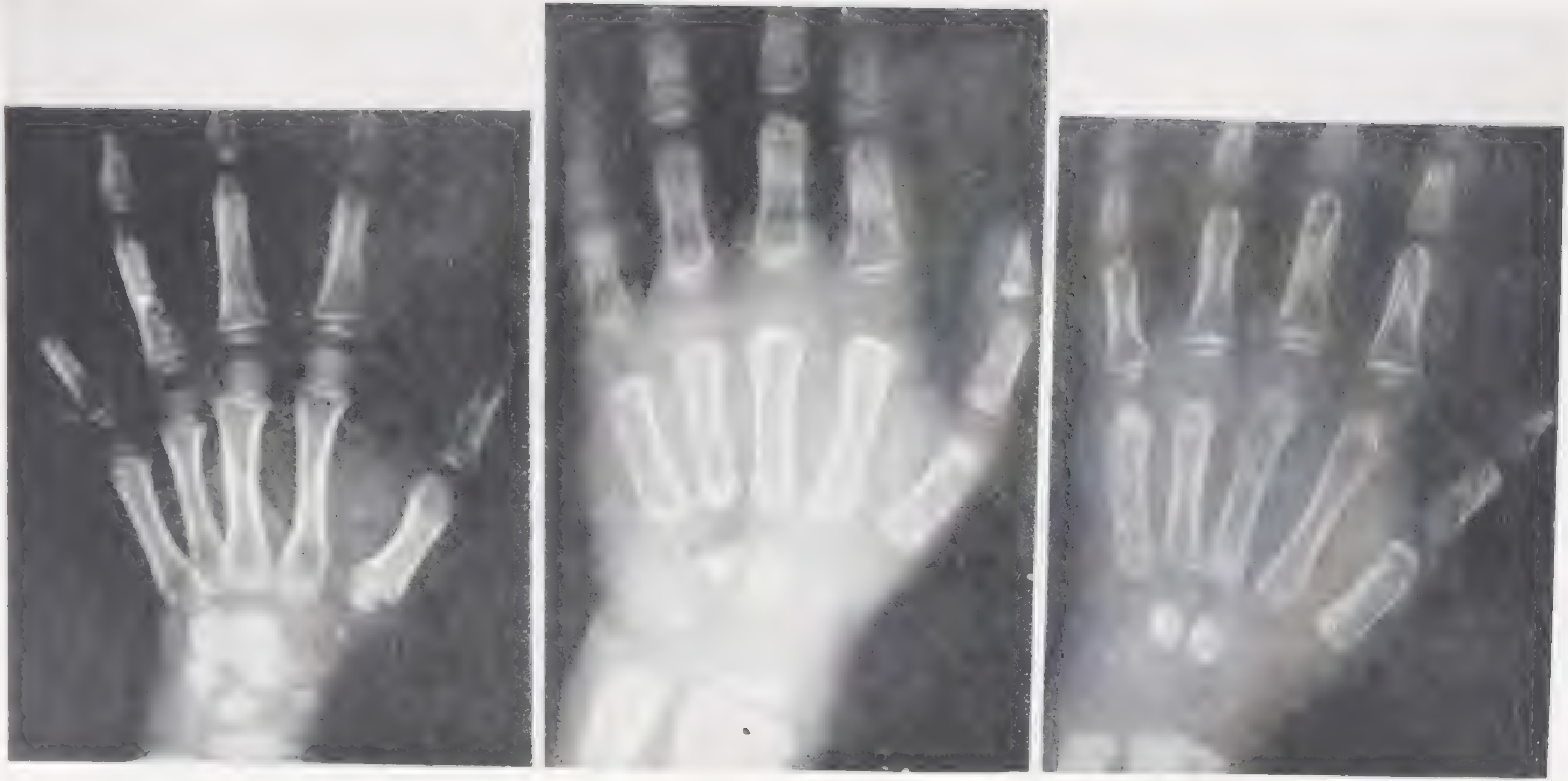


2

Section of heart from a case of adult nutritional oedema, showing diffuse fibrosis

(By courtesy of Dr V. Ramalingaswami, Pathologist, Nutrition Research Laboratories, Coonoor

PLATE 19

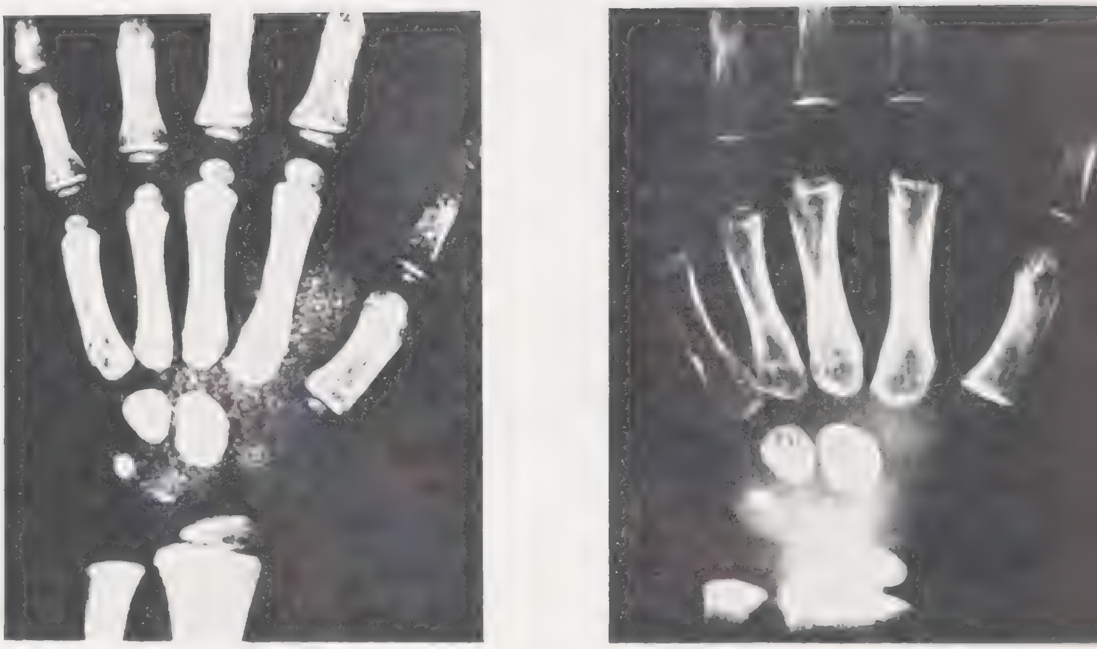


1 2 3

1. X-ray of the wrist from a normal child aged 3 years 10 months. 2. X-ray of the wrist from a case of kwashiorkor, aged 3 years 10 months. 3. X-ray of the wrist from a case of kwashiorkor, aged 3 years 10 months.

(By courtesy of Dr K. Someswara Rao, Field Officer, Nutrition Research Laboratories, Coonoor.)

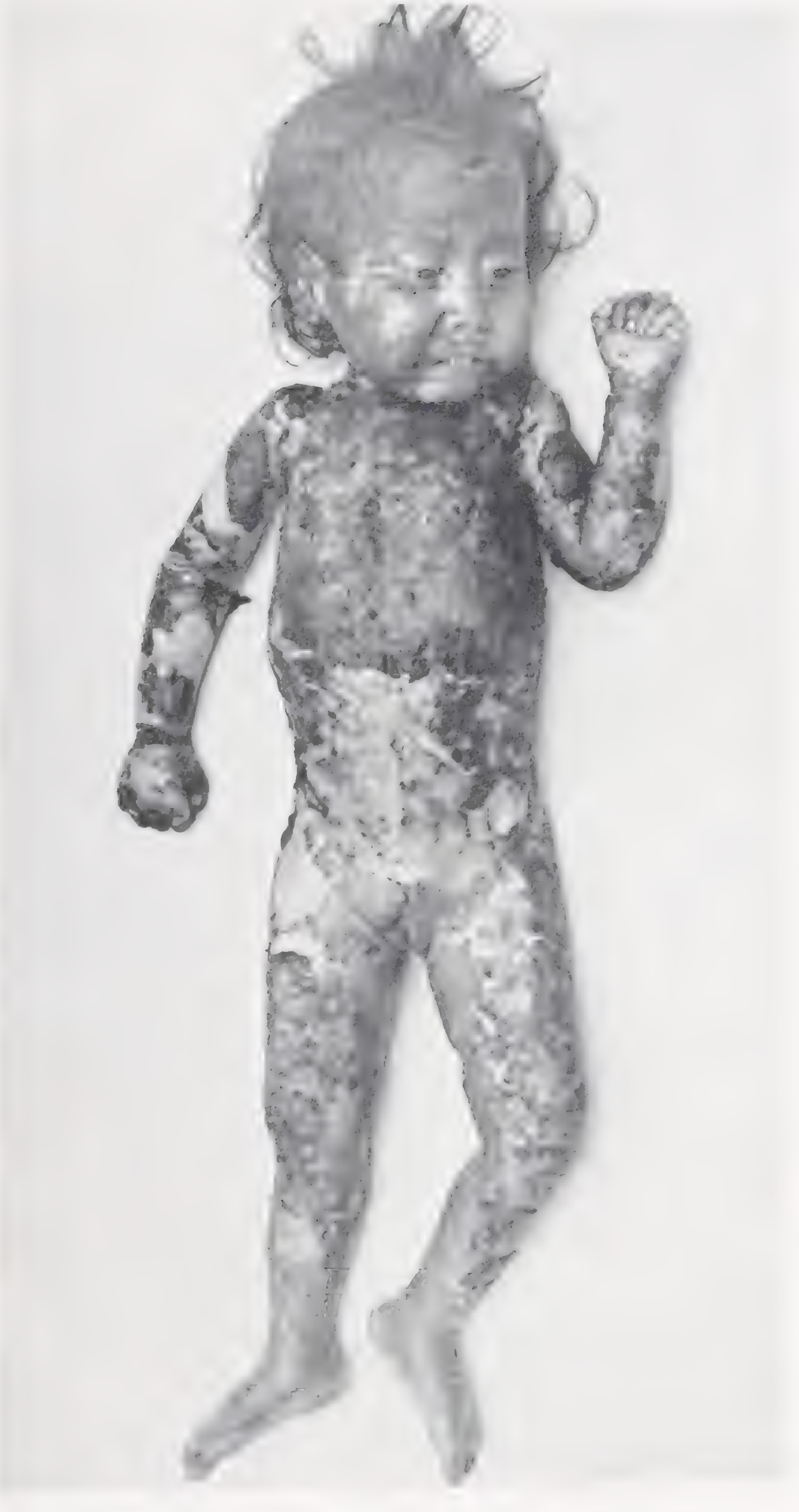
PLATE 20



1

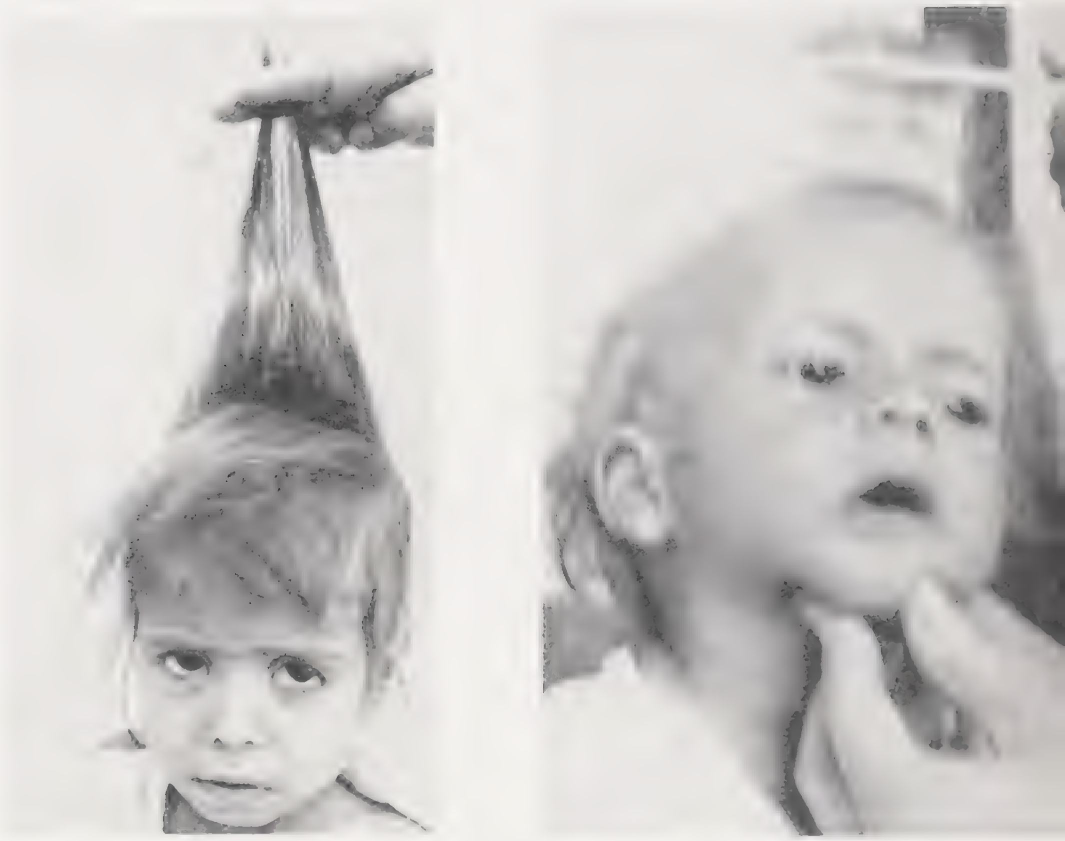
2

1. X-ray of the wrist from a normal child of 3 years (Greulich & Pyle (11)). 2. X-ray of the wrist from a Guatemalan school-child, not obviously ill. Height 100 cm. Weight 32·5 kg. Chronolog age 9 years, bone age 3 years. This represents an extreme case of bone-age retardation



Guatemalan girl aged 5 years. To show hyperpigmentation and desquamation of the skin over the whole body.

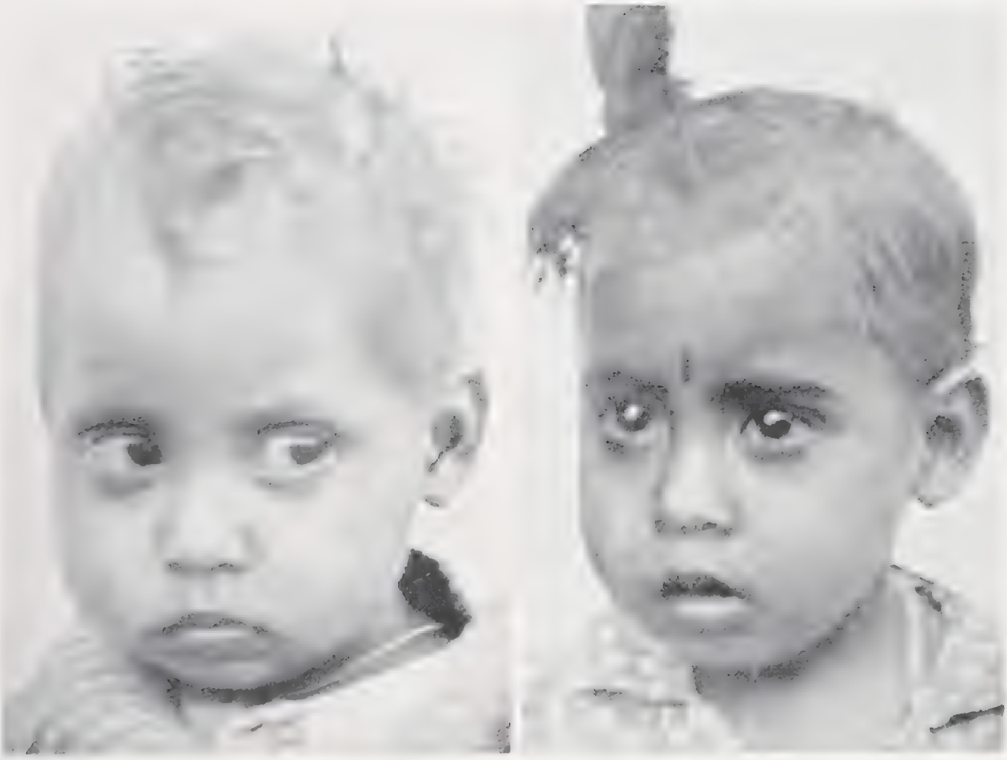
PLATE 22



1

2

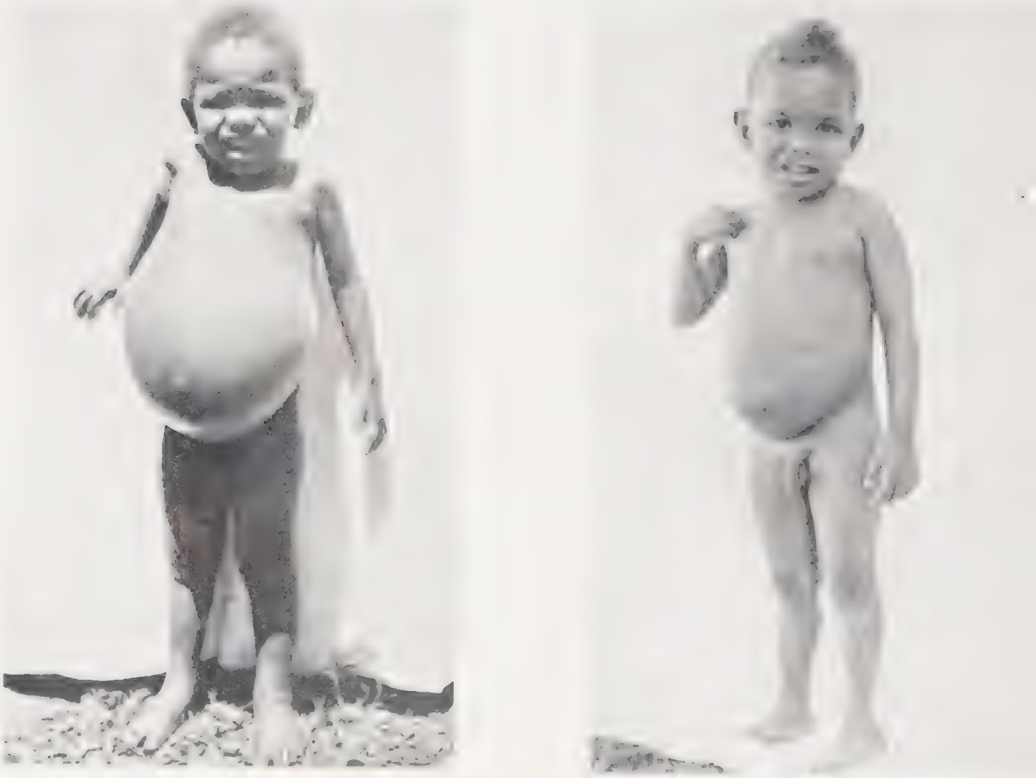
Depigmentation of the hair. Hospital San Juan, Costa Rica. 1. This girl, 7 years old, readmitt to the hospital for acute dysentery, shows in the hair a whitish band caused by a period of m nutrition. The patient was admitted 10 months before the picture was taken for a typical multip deficiency syndrome. 2. This child, 2 years old, had several episodes of severe malnutrition th corresponded to the two whitish strips shown in the hair. The middle and the proximal blacki bands correspond to periods of hospital care and good diet.



(A) (B)

'Moon-face' in an undernourished child without oedema (A) before and (B) after treatment with skim milk.

PLATE 24



(A) (B)

Boy initially aged 2 years, with V.O.D., before (A) and after (B) treatment with ventriculin.

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